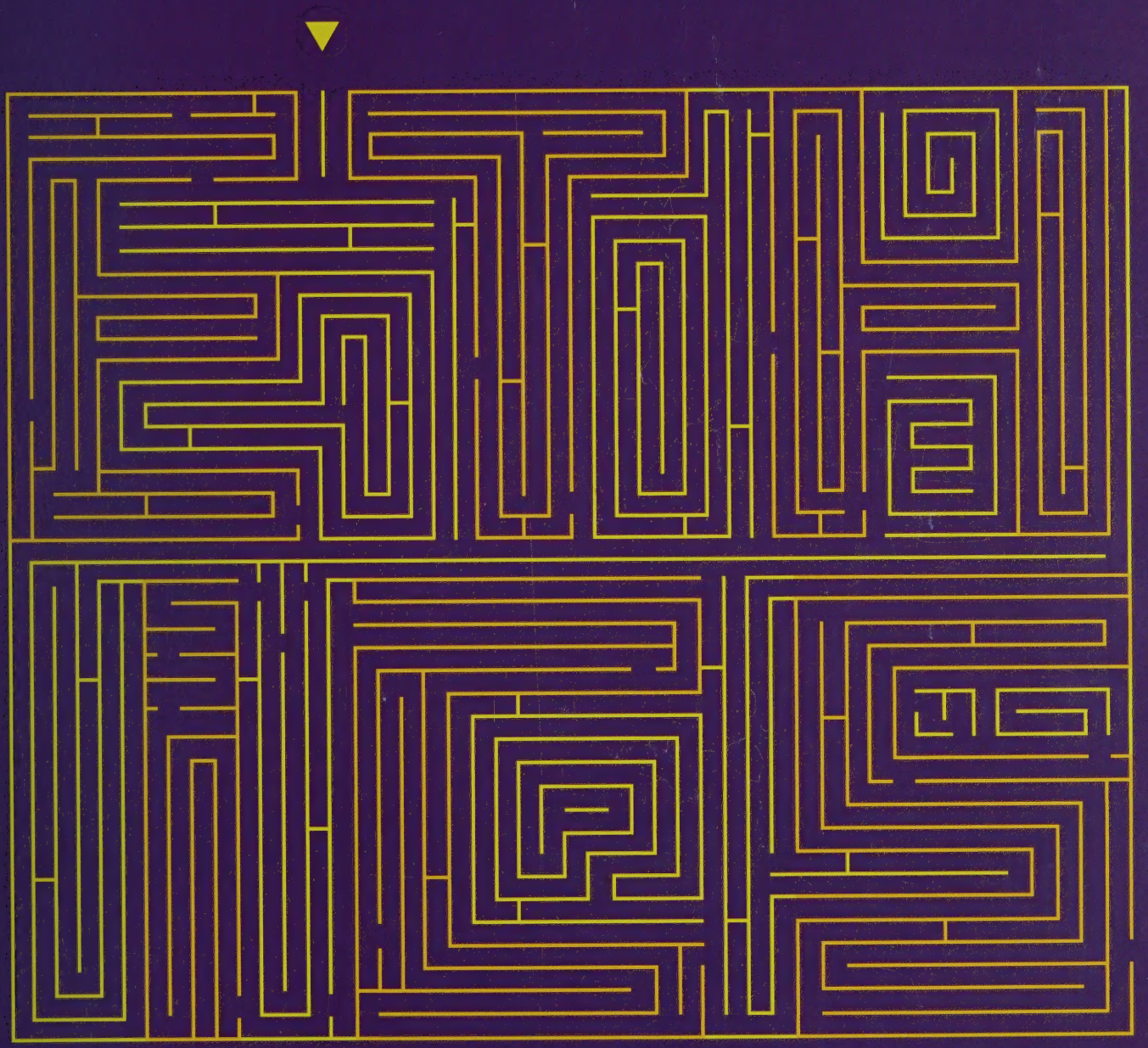
Harvard Medicine

AUTUMN 2016



Navigating the twists and turns of medical ethics tests researchers and physicians

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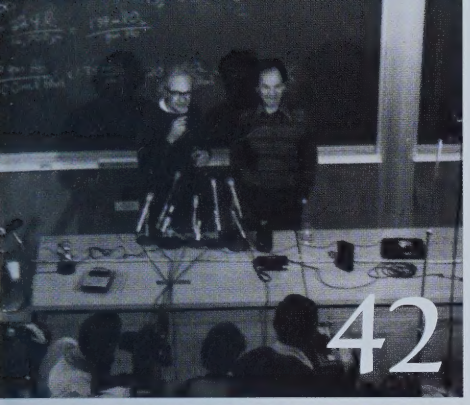
AFTERMATH: The need to triage care for the injured following catastrophes is captured in this drawing of hospital attendants caring for the wounded after the Civil War engagement at Hatcher's Run.

Night after Battle* 1864, *Harper's Weekly
Pencil, Chinese white, and black ink wash on brown paper



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From the Dean

NOT SO LONG AGO, Harvard researchers found what they called the morning morality effect; that is, it's easier for us to resist moral temptations in the morning, before what the researchers described as the cumulative effect of the day's unremarkable experiences deplete our moral reserves.

This might give physicians pause. Our day-to-day activities, whether in the clinic or the laboratory, are filled with dilemmas that challenge our training in how to make ethical decisions—and our moral fiber.

To help safeguard ourselves from this apparent circadian cycle, we train and we teach. A glance at the topics our first-year students confront in the Pathways curriculum's social and population sciences courses gives insight into the range of issues the School helps them prepare for: truth-telling, reproductive ethics, patients' capacity for informed decision making, informed consent, and confidentiality.

Our physician-researchers also prepare, many as they were themselves prepared: ensure the work is safe before it's broadly applied, be a voice for responsible science, and train the next generation to excel as researchers and as science-savvy members of the public.

We look at these and other ethical aspects of medicine in this issue of *Harvard Medicine*. Experts weigh in on the relevance of the dead-donor rule given advances in life-sustaining technologies and our understanding of the growing difficulties of knowing when the heart or the brain truly stops functioning. Others discuss the ethics of access to reproductive technologies, and one, an alumna, considers the responsibilities that physician-writers have to patients and their stories.

We also take a moment to celebrate an anniversary. The HMS Department of Neurobiology is marking its fiftieth year. Those many decades ago, it became the first academic department in the nation to take a multidisciplinary approach to the study of the brain. It remains a strong example of the vision and innovation that underlie the work of our Quad scientists.

Barbara McNeil

Barbara McNeil
Acting Dean of the Faculty of Medicine
Harvard University

HarvardMedicine

Editor
Ann Marie Menting

Design Director
Paul DiMattia

Assistant Editor
Susan Karcz

Senior Graphic Designer
Jill Carrico

Contributing Writers
Elizabeth Cooney, Laura DeCoste, Elizabeth Dougherty, Stephanie Dutchen, Nancy Fliesler, Kate Harper, Courtney Howe, Katherine Igoe, Perri Klass, Sue McGreevey, Jake Miller, Ekaterina Pesheva, Michael Rafferty, Sara Silvestro

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JOHN SOARES

Letters to the Editor

CHART NOTES FROM OUR READERS

Guiding Light

It has been a long time since I was a student at HMS and was accepted into the School's Health Sciences and Technology program; a long time ago when, as a native Swiss, I struggled with the descriptive English that is so relevant in medicine but not much required in physics. But, after reading "A View of London" in the Spring 2016 issue of *Harvard Medicine*, I realized the 40-year-old memories are still vivid.

Being an HST student was the key experience in my academic life. A small number of professors—Irving London '43, with his vision of bringing medicine, science, and engineering together; the late Walter Abelmann; George Benedek, my PhD thesis supervisor; and Felix Villars, among others—had crafted a medical curriculum that was unique and uniquely suited to me. With my love for medicine and enchantment with physics, I found the HST program was my golden path to becoming an MD-PhD. HST made me resilient enough to tackle an academic career, to strive for excellence, and to not leave difficult problems to others.To echo President Barack Obama's campaign slogan, it taught me to say "yes, I can!"

Having a Harvard MD and a physics PhD from MIT opens doors in the United States, but not in other countries. I remember my chief of medicine at the University Hospital of Zurich summarizing my education but forgetting to mention my doctorate in physics from MIT. For that moment, the omission shattered me. But eventually I came to realize that ultimately it was not the diplomas that counted, but instead, the spirit of the schools you have the opportunity to attend and the spirit that forms your academic character and allows you to accomplish things.

In addition (and this was so critical for me), the professors at Harvard and MIT were humble. Even today, I sometimes miss finding that quality in others in my environment. Those professors were willing to listen to the dumbest questions, answering patiently and in a manner that supported us in our learning process. At a critical moment in my development as a medical and science professional, I was measured not by my academic medical knowledge, which was pretty poor, owing to my hefty engagement in work for my PhD, but rather by my potential. This is what I think was and, with hope, still is the spirit of HST.

HST made me resilient enough to tackle an academic career, to strive for excellence, and to not leave difficult problems to others.

GUSTAV VON SCHULTHESS '80
ZURICH, SWITZERLAND

During my years with the program, HST provided an environment in which young people, all willing to give their best while getting an education, were supported and, in fact, encouraged, to pursue their education in multiple original and special ways even if they did not excel in all the required fields. This was the spirit fostered by Irving London. I remain greatly indebted to him, even now, as I begin to retire from my own academic endeavors.

GUSTAV VON SCHULTHESS '80
ZURICH, SWITZERLAND

Forward, and in Heels

I read with interest the "Stress Fractures" article in the Spring 2016 issue of *Harvard Medicine*. It caused me to reflect on my own interview day.

Although the era of the "stress interview" had ended by 1977, the year I interviewed at HMS, the folks in the admissions office may have been taking careful notes during the previous years.

On the morning of my interview, my sister battled traffic to drive me from Cambridge to the admissions office at HMS. I arrived just in time, but was told that my first interview would in fact be in an office on Brattle Street in Harvard Square. The secretary waved me vaguely in the direction of Huntington Avenue and off I went. Those were the days before smartphones, but, even so, it seemed like it would be easy to navigate my way back to Cambridge and fairly easy to find Brattle Street. I was within minutes of my goal—or so I thought.

As I passed the addresses on Brattle Street, I noticed the numbers weren't advancing quite as quickly as I would have expected. Time was passing. There were no cabs so I started running—in heels and a restrictive skirt. I stuck my thumb out in hopes of a ride.

I covered maybe three-quarters of a mile before hitching a ride, one that covered what I felt was about an equal distance. I was late, quite late, but managed to joke about it to the kindly psychiatrist who would interview me. Secretly, I was freaking out.

With that interview completed, I had to head to the second one. Where? Back on the medical school campus, of course. But there was a gap between the interviews so I had ample time and succeeded in making it to the next one on time.

After catching my breath from the day, I was left with a good story—and several months of physical therapy for knee pain secondary to having run in heels.

Was the day a test of my ingenuity and calm under pressure? Was it carelessness, callousness, or black humor on the part of the admissions committee? I leave you to ponder these questions yourself. I've gotten over it.

BETH SCHWARTZ '82
BALTIMORE, MARYLAND

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*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.*

SECOND TIME AROUND

HMS again turns to alumna Barbara McNeil at a time of transition

BARBARA MCNEIL'S HMS diploma bears the signature of Dean Robert Ebert, a physician who stayed at the School's helm through McNeil's pediatrics internship at Massachusetts General Hospital, her radiology residency at the former Peter Bent Brigham Hospital, and her early years as a junior faculty member at HMS. Then the leadership shifted from Daniel Tosteson '48 to Joseph Martin to Jeffrey Flier while McNeil moved up the faculty ladder, ultimately becoming the founding chair of the HMS Department of Health Care Policy.

Thus, McNeil has been a vital part of HMS for five decades and a witness to the decanal tenures of four men: Ebert, Tosteson, Martin, and Flier.

And one woman: herself. "Twice," she adds.

Barbara McNeil '66, HMS acting dean, is indeed marking the second time she has accepted the call to serve the institution that formed her as a physician-scientist and has benefited from her skills as a leader in research, policy, and education. She will remain acting dean until January 1, 2017, when George Q. Daley '91 will take office as the twenty-second dean of HMS.

According to McNeil, being an alumna of the School is an important plus for the role she's taken on.

"I think it's quite useful for someone who graduated from this school and who has been in this environment as a physician, a researcher, and a teacher to take on its leadership during this time of transition. I know the language of this complex institution, and I know its history for the past half century. I think both can contribute to the needs of this community."

Community is the key to McNeil's tenure as acting dean.

"I think it's critical that faculty at HMS feel closely aligned with the School's administration, as well as with that of Harvard," she says. "In fact, I think increasing the involvement of the faculty, their sense of community, and the ease with which they can collaborate, are important tasks for me during the next few months.

"Building and facilitating community for our students is also vital. Students now learn in settings that depend on collaboration and exchange. If I can help that sense of community, that sense of bonding, to increase, I will feel my months as acting dean will have contributed to the School's continued vitality."

Above everything, McNeil is pleased to once again have the privilege of guiding the school that guided her professional development. "We are fortunate to be able to pursue our work at this remarkable institution," says McNeil. "I'm honored to have this opportunity to serve the faculty, students, and staff of HMS."

—Ann Marie Menting

The 2020 class of Harvard Medical School and Harvard School of Dental Medicine gathered in the atrium of the Tosteson Medical Education Center on Orientation Day.

A 2020 Look at the Future

IN EARLY AUGUST, members of the Harvard Medical School and Harvard School of Dental Medicine Class of 2020 slipped on new white coats, welcome gifts from the Aesculapian Society.

Speakers at the white coat ceremony reminded the new students of the importance of learning to listen—to both their patients and to their own inner voices.

Fidencio Saldaña '01, HMS dean for students, asked the students who assembled in the Carl Walter Amphitheater to close their eyes and picture a moment that symbolized their reasons for becoming doctors.

"Ingrain that picture in your mind's eye and don't ever forget it," Saldaña said. "In good times and in bad times, you can celebrate that picture and find the strength to go on."

HMS Acting Dean Barbara McNeil '66 added encouraging words, saying, "Within this community that you are joining, there is an unmatched depth and breadth of work being done to meet the challenge of improving human health.

"No matter what aspects of this mission call to you most deeply, you will find partners and a home here."

This year's incoming class of HMS students includes eighty-four women and eighty-one men selected from a pool of more than 7,000 applicants. They represent thirty-five U.S. states and eight foreign countries and come from sixty-five different undergraduate institutions.

Students who identified themselves as being from groups underrepresented in medicine (Black, Hispanic, Mexican American, Native American, and Puerto Rican) account for 16 percent of the incoming HMS class.

—Susan Karcz and Jake Miller

Welcome to Gordon Hall

HMS alumnus named School's new dean

GEORGE Q. DALEY '91 has been named the twenty-second Dean of the Faculty of Medicine, Harvard University. A longtime member of the HMS faculty and a researcher of note in the field of stem cell science and cancer biology, Daley officially begins his appointment on January 1, 2017.

In accepting the deanship, Daley said he was "humbled by the prospect of leading so talented a community with so essential a mission—a community whose dynamism, growing diversity, and shared concern for the well-being of others are a deep source of strength."

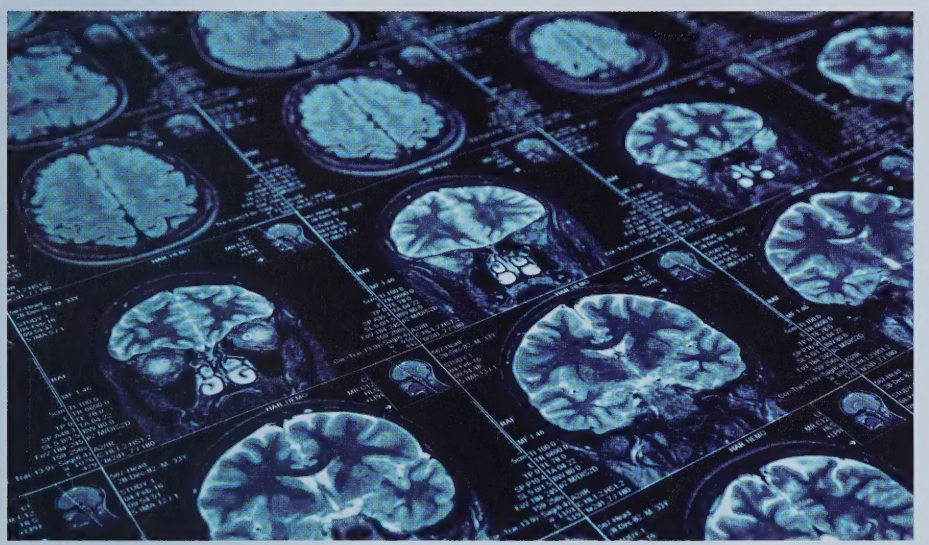
A graduate of Harvard College ('82) and HMS, with a PhD in biology from MIT, Daley currently serves as an HMS professor of biological chemistry and molecular pharmacology and as the School's Robert A. Stranahan Professor of Pediatrics. He also is the director of the Stem Cell Transplantation Program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center.

In announcing Daley's appointment, Harvard President Drew Faust described him as "an eminent scientist, a dedicated educator, an adept bridge-builder, a compelling advocate for scientific discovery, and a person of remarkable leadership qualities and thoughtful judgement."

Harvard Provost Alan Garber addressed some of the qualities that made Daley so suitable for his new role, "[Daley] is a remarkable scientist and an equally remarkable person, as humane and collegial as he is intelligent and accomplished."

Faust and Garber expressed particular thanks to the search advisory committee, a group that represented preclinical departments, the affiliated hospitals, and the University, saying that its members helped them "arrive at an excellent outcome."

In its Winter 2017 issue, *Harvard Medicine* magazine will talk with Dean Daley about his vision for the School.



Picture Perfect

Digital tool will provide evidence-based aid to clinicians ordering imaging tests

DOES A YOUNG woman's recurring flank pain warrant a CT scan or is she better off undergoing an ultrasound?

To help clinicians choose the most appropriate imaging test for a patient, HMS is launching the Library of Evidence, a publicly accessible digital repository of medical evidence. Initially focused on imaging, the long-term goal of the database is to include laboratory testing and other medical procedures that require evidence-based support tools.

"The overarching goals are to improve patient care and curb wasteful imaging by optimizing clinicians' ability to choose the most appropriate imaging," says David Osterbur, director of Public and Access Services at the Francis A. Countway Library of Medicine and co-executive director of the Library of Evidence.

Adds Ramin Khorasani, an HMS professor of radiology at Brigham and Women's Hospital and chair of the new library's governing council, "The library is an important step toward organizing what is known to help advance the goal of evidence-based practice in a concrete way."

The Library of Evidence database contains clinical information compiled from the review and scoring of scientific evidence, published research, and professional organizations' imaging guidelines.

Free and accessible to clinicians worldwide, the library can be embedded into various clinical information systems used by individual practices and hospitals. If a physician is ordering a CT scan for a patient with back pain, for example, the system might indicate an ultrasound instead and provide evidence-based recommendations as support for the analysis.

In an era of rushed appointments, physicians may have become overly reliant on imaging. The Library of Evidence is designed to curb this practice by providing clinicians with readily accessible medical evidence for each clinical scenario.

The most important benefit of evidence-based decision making, the HMS team says, is improving quality of care.

The launch of the library may be particularly timely for clinicians caring for Medicare and Medicaid patients. Federal legislation requiring clinicians to consult "appropriate-use" criteria using certified decision-support systems is slated to go into effect in 2018.

Information for physicians can be viewed at libraryofevidence.med.harvard.edu/resources.html#professionals.

—Ekaterina Pesheva

William Kaelin Receives 2016 Lasker

HMS scientist recognized for pivotal discovery in cells' response to oxygen deprivation

WILLIAM KAELIN JR., an HMS professor of medicine, has been named a recipient of the 2016 Lasker Award for Basic Medical Research from the Albert and Mary Lasker Foundation. The Lasker is one of the world's most prestigious biomedical research awards.

Kaelin, based at Dana-Farber Cancer Institute, was cited along with Peter Ratcliffe of the University of Oxford/Francis Crick Institute and Gregg Semenza of the Johns Hopkins University School of Medicine, for the discovery of the pathway by which cells from humans and most animals sense and adapt to changes in oxygen availability—a process essential for survival.

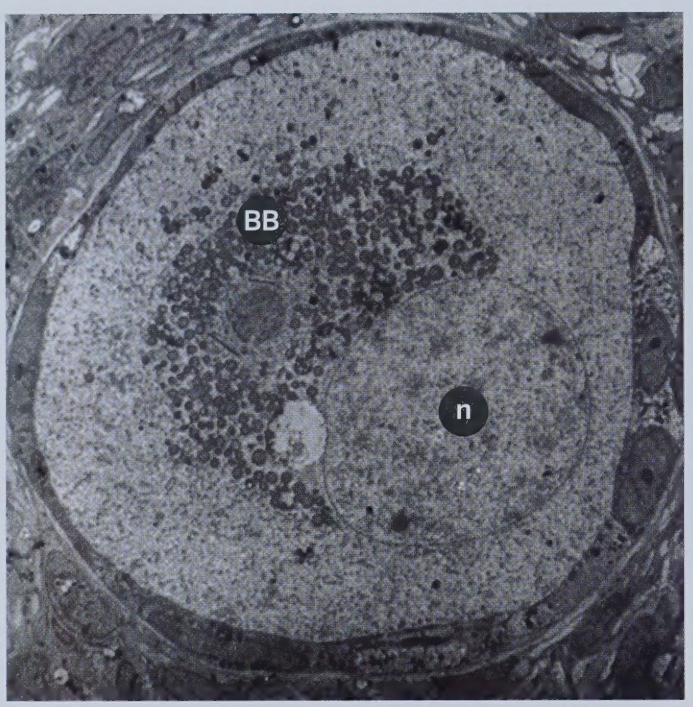
"Bill Kaelin is an outstanding physician, scientist, and educator," said Barbara McNeil '66, acting dean of HMS. "I am delighted that his extraordinary dedication, his years of hard work, and his remarkable discoveries have been recognized by the Lasker Foundation."

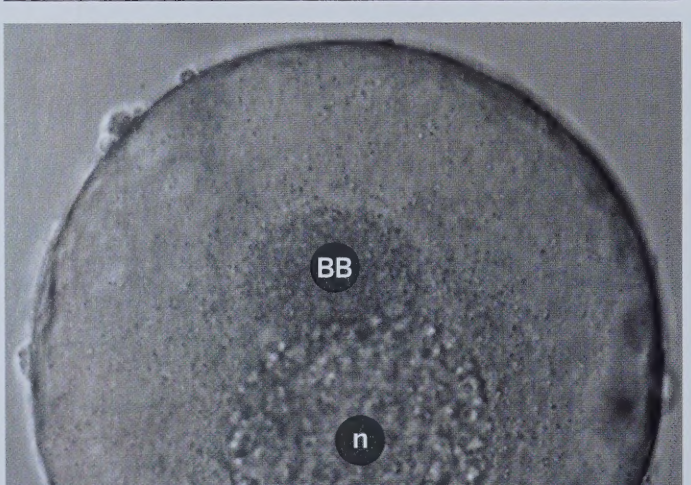
Kaelin's research explores why mutations in tumor-suppressor genes can lead to cancer. His study of a tumor-suppressor gene called *VHL* provided key insights into the body's response to changes in oxygen levels.

Kaelin discovered that *VHL* helps control the levels of a protein known as HIF, which regulates responses to low oxygen levels, such as in the production of red blood cells and new blood vessels.

His subsequent discovery of a molecular switch that renders HIF oxygen sensitive was critical to the understanding of how cells react to variations in oxygen level.

For 71 years, the Lasker Awards have recognized the works of scientists, clinicians, and public citizens who have advanced the understanding, diagnosis, treatment, cure, or prevention of human disease. Eighty-seven Lasker laureates have received a Nobel Prize, including forty-one over the past three decades.





In the months or years before an egg matures, Balbiani bodies (BB) hold organelles together in a spot next to the nucleus (n). Pictured here are a human egg (top, enlarged) and an immature frog egg.

Tidy Package

"Super-organelles" use amyloids to bundle contents in immature egg cells

RESEARCHERS DON'T YET KNOW how immature egg cells, or oocytes, survive and protect their contents while they lie dormant for years in a woman's ovaries, awaiting hormonal signals that ready them for fertilization.

But clues, say cell biologist Elvan Boke and her colleagues at HMS, might lie in Balbiani bodies.

The Balbiani body is one of the more striking features of an oocyte, although it has been slow to reveal its secrets. Scientists know that it is a membraneless ball made up of mitochondria, other organelles, and proteins, and that it breaks apart when the oocyte begins maturing into an egg, releasing the organelles into the cytoplasm.

"How do they form and disperse?" asks Boke, who is a postdoctoral researcher and first author of the study. "How do they stay together without a membrane? What is their biological function?"

Boke, together with colleagues at HMS and the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany, reported online in *Cell* on July 28 that in the oocytes of *Xenopus* frogs, long a model organism for fertility research, the contents of Balbiani bodies are bound together by a protein called Xvelo that clumps into a dense network of amyloid fibers.

"Amyloids have a scary reputation as the causative agents of neurodegenerative diseases, but we know relatively little about their possible normal functions," says Timothy Mitchison, the Hasib Sabbagh Professor of Systems Biology at HMS and senior author of the study. "Xvelo provides one of the few emerging examples of a normal amyloid."

Because Xvelo loses its amyloid-like configuration as the egg matures, the researchers think the frogs' Balbiani bodies could hold clues for how to break up toxic amyloids seen in human diseases such as Alzheimer's and ALS.

At a fundamental level, the study is notable because the team "found that cells can use a protein to create a compartment from scratch," says Boke. "This scale of cytoplasmic organization hadn't been reported before."

"We think the dormant oocyte packs away the majority of its organelle and RNA content when it's not needed," Boke adds. "It's unpacked when the oocyte activates and it's time to use them."

If further research shows that Balbiani bodies are indeed critical for keeping eggs viable for long periods of time, it could have implications for human egg freezing and fertility treatments.

Although Xvelo isn't well conserved in evolution, it does have counterparts—Bucky ball in zebrafish, Oskar in fruit flies—that are responsible for organizing Balbiani bodies or similar structures. Despite different genetic sequences, those proteins have something in common: a portion of their structure—a prion-like domain—that makes them likely to self-assemble.

The researchers found that Xvelo has such a domain, too. When they removed it by mutating the gene for Xvelo, the protein no longer aggregated.

"Pathological amyloids don't go away," says Boke, "but those in Balbiani bodies dissolve when the oocyte matures. This could be important for understanding how to make 'bad' amyloids disappear." —*Stephanie Dutchen*

ARTHUR HERTIG (TOP PAR LEFT), ELVAN BOKE (BOTTOM)

THE LONG VIEW

Postoperative delirium could warn of long-term cognitive decline among older patients

DELIRIUM IS A COMMON, serious, often fatal disorder that affects as many as 50 percent of older people during the course of surgery or hospitalization. Yet, despite delirium's incidence among elderly hospitalized patients, its relationship to long-term cognitive decline has not been well explored.

In the July 2016 issue of *Alzheimer's & Dementia*, however, researchers from HMS and Hebrew SeniorLife Institute for Aging Research report that there is increasing evidence that delirium in older surgical patients may be associated with such cognitive decline. The study, conducted in collaboration with scientists at Beth Israel Deaconess Medical Center, Brown University, and Northeastern University, examined the trajectory of short-term and long-term cognitive decline in patients who experienced post-surgical delirium.

The study involved 560 participants, each age 70 or older and each without previous signs of dementia, who were scheduled to undergo surgery with an anticipated hospital stay of three days or more.

Over 36 months following their surgeries, 134 patients experienced delirium. Those who experienced delirium as well as those who did not showed a significant cognitive decline at one month, a recovery above baseline at two months, then a gradual decline during the following 34 months. Yet those who had experienced delirium showed a significantly greater decline at one month compared to those without delirium. Although they too recovered at two months, the patients who experienced delirium had a more significant decline after the two-month mark than patients who did not experience delirium. Beyond two months, both groups declined on average, but the delirium group declined significantly more. When researchers compared changes from baseline to 36 months, there was no significant change in the group that did not experience delirium, but there was a marked decline in the group that did. *—Courtney Howe*

Hoop Dreams

Discovery of new bacterial cell wall builders may offer target for antibiotic development

SCIENTISTS HAVE IDENTIFIED a new family of proteins that virtually all bacteria use to build and maintain their cell walls. The discovery of a second set of cell wall synthesizers may inform development of much-needed antibacterial therapies, say study leaders David Rudner and Thomas Bernhardt, both professors in the HMS Department of Microbiology and Immunobiology. Their research team reported its work online on August 15 in *Nature*.

Made up of chains of sugars linked by short peptides, a bacterium's cell wall plays a critical role in maintaining its structural integrity, dictating its shape, and repelling external assaults from toxins, drugs, and viruses.

Penicillin-binding proteins—molecules named for the drug that disables them—were long thought to be the major, perhaps only, cell wall synthesizers. The fact that these proteins were integral to cell wall construction was revealed in the late 1950s, but the mechanism behind their action was not unraveled until the 1970s and 1980s in research using the bacterium *Escherichia coli*.

Clues that other players may be involved in cell wall biogenesis emerged later. Tsuyoshi Uehara, a former HMS research fellow in the Bernhardt lab and co-author of the paper, thought a family of proteins responsible for a cell's shape, elongation, division, and spore formation—SEDS proteins in scientific shorthand—could be an unidentified player.

SEDS proteins move around the circumference of the bacterial cell. If the proteins are inactivated, cell wall synthesis is perturbed.

In genetic and biochemical experiments, the research team confirmed that SEDS proteins were a new family of cell wall synthesizers that behaved in a different yet complementary way from the penicillin-binding proteins. SEDS proteins circumnavigate the cell wall, making hoop-like structures, while penicillin-binding proteins move diffusely, making smaller strands that, together with the hoop-like strands, build the cell wall.

In the current paper, the scientists found that SEDS proteins are more common in bacteria than are the penicillin-binding proteins, raising hopes that a potential antibiotic targeting SEDS proteins could be effective against a broad spectrum of bacteria.

—Elizabeth Cooney

Lines show movement of SEDS protein complex

Hypertrophic cardiomyopathy

Broader Reach, Better Diagnoses

Genetic tests for potentially fatal heart anomaly can misdiagnose condition in U.S. Blacks

GENETIC TESTING has greatly improved physicians' ability to detect potentially lethal heart anomalies among family members of people who suffer cardiac arrest or sudden cardiac death.

Researchers in the HMS Department of Biomedical Informatics have, however, found that over the past decade these lifesaving tools may have disproportionately misdiagnosed one cardiac condition—hypertrophic cardiomyopathy (HCM)—in Blacks. HCM, which affects one in 500 people, is an often-asymptomatic thickening of the heart muscle that can spark fatal arrhythmias in seemingly healthy young adults.

The study appeared in the August 18 issue of the *New England Journal of Medicine*.

Although it is recognized that genetic tests can misread benign genetic alterations as disease-causing mutations, this study may be the first one to link the problem to racially biased methodologies in early studies that defined certain common genetic variants as causes of HCM.

The analysis reveals that the misdiagnoses of HCM stemmed from clinical studies that used predominantly white populations as control groups.

Whites harbor fewer benign mutations on several genes implicated in HCM than do Blacks. The higher rate of benign alterations in the latter group can cause test results to be misread as abnormal, the researchers say.

The HMS team demonstrated that including even small numbers of Black participants in the original studies would have improved test accuracy and, consequently, helped avert some of the misdiagnoses.

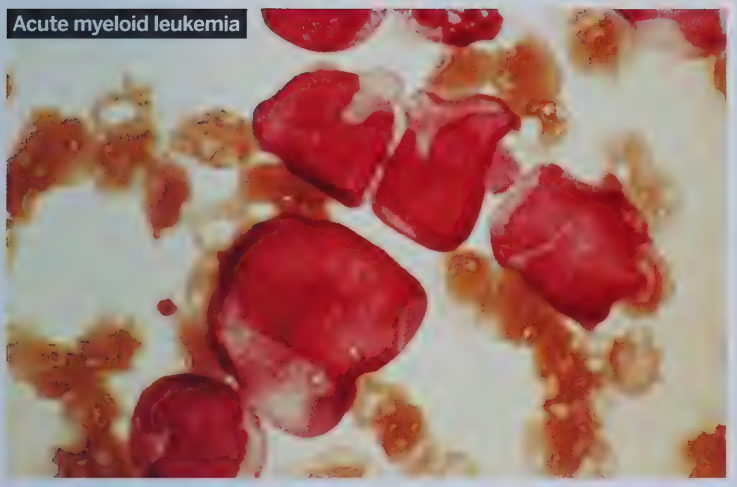
The findings, the researchers say, highlight the importance of interpreting genetic test results against diverse control populations to ensure that normal variations of genetic markers common in one racial or ethnic group do not get misclassified as disease-causing in another.

"We believe that what we're seeing in the case of hypertrophic cardiomyopathy may be the tip of a larger problem that transcends a single genetic disease," says study first author Arjun Manrai, a research fellow in the Department of Biomedical Informatics. "We hope our study motivates a systematic review of this issue across other genetic conditions."

Aside from the emotional toll that a genetic misdiagnosis can take on individuals and families, the researchers say their findings represent a cautionary tale with a broad relevance to geneticists, clinicians and policymakers alike.

"Our study powerfully illustrates the importance of racial and ethnic diversity in research," says Isaac Kohane, senior investigator on the study and chair of the department. "Racial and ethnic inclusiveness improves the validity and accuracy of clinical trials and, in doing so, can better guide clinical decision making and choice of optimal therapy. This is the essence of precision medicine."

—*Ekaterina Pesheva*


Acute myeloid leukemia

More Fat, Please

Cancers' taste for fat may be proved to be their Achilles' heel

CANCERS ARE SUCH notorious sugar addicts that PET scans searching for the disease light up when they detect sugar-gobbling tumor cells. But a handful of cancers appear to favor fat over sugar, a fact that has long mystified scientists. Now, an HMS study shows how certain tumors develop a taste for fat as their life-sustaining fuel.

The findings, published September 15 in *Molecular Cell*, show how a signaling pathway that normally keeps fat-burning in check goes awry in some cancers, revving up fat consumption and fueling tumor growth.

The study found that the protein prolyl hydroxylase 3 (PHD3) appears to be key to regulating cellular mechanisms that dampen fat-burning. That protein, the research shows, is abnormally low in certain forms of cancer, including acute myeloid leukemia and prostate cancer.

Biologists have known for some time that when cells run low on nutrients they switch from burning sugar to burning fat for fuel.

When cells have low energy, the protein AMPK targets an enzyme, ACC, to activate fat oxidation, which helps cells burn fats to make energy. The team wanted to know how cells turn off fat oxidation.

They homed in on the protein PHD3; a handful of recent studies had suggested it plays a role in cell metabolism.

In a series of experiments, the HMS research team showed that PHD3 suppressed fat-burning by chemically modifying and activating a version of ACC responsible for keeping cellular fat-burning in check. When the scientists restored to normal the levels of PHD3 in a line of cancer cells and in mice, the tumors not only stopped growing, they died.

"This really represents a new frontier in looking at the metabolism of cancer," says Marcia Haigis, an HMS associate professor of cell biology and senior author of the paper. "This is one of the few pathways we've modulated where we really see the tumors die. They are so dependent on fat oxidation that they die."

—Elizabeth Cooney

PR. J. BERNARD/CNRI/SCIENCE SOURCE; ISTOCK (FAR RIGHT)

Keep Calm

Moving to electronic records does not adversely affect short-term inpatient outcomes

AS WAVES OF HOSPITALS move from older methods of record keeping to new electronic health record (EHR) systems, many medical professionals express fears that implementing an EHR system in their hospital will have dire results, including more errors and higher patient mortality.

But these fears are largely unfounded, according to research published in the July 28 issue of *The BMJ* by researchers from HMS and the Harvard T.H. Chan School of Public Health who studied a diverse group of U.S. hospitals that implemented new EHR systems in 2011 and 2012.

These researchers found that among patients treated at 17 U.S. hospitals launching an EHR system during the study period, there was no short-term increase in inpatient mortality, adverse safety events, or readmissions compared with data from a control group of nearly 400 hospitals within the same referral region. Each of the seventeen hospitals with a new EHR system had implemented it in a single day, making it possible for the researchers to analyze patient outcomes using Medicare data from before and after the "go live" days in each hospital and compare them with data from other hospitals.

The investigators also found no change when examining data from hospitals that might have been at higher risk for problems such as sicker patients or hospitals that transitioned from paper to electronic charts, versus those that simply switched from one electronic system to another.

"Having witnessed firsthand how disruptive an EHR implementation can be," says Anupam Jena, senior author of the study and the Ruth L. Newhouse Associate Professor of Health Care Policy at HMS, "it is reassuring to know that hospital safeguards prevent patients from being harmed."

—Katherine Igoe

Bacterial colonies growing within antibiotic-dosed medium

They're Alive!

A supersized view of bacterial mutation shows evolution in action

IN A CREATIVE STROKE inspired by Hollywood marketing wizardry, scientists from HMS and Technion-Israel Institute of Technology have designed a simple way to observe the life and death struggles of bacteria as they encounter, and often adapt to, increasingly higher doses of antibiotics. The experiments, described in the September 9 issue of *Science*, are thought to provide the first large-scale glimpse of bacterial mutation.

To capture this, the team constructed a 2-by-4-foot petri dish and filled it with 14 liters of agar, a seaweed-derived jellylike substance commonly used in labs to nourish organisms as they grow. They called the monster plate the Microbial Evolution and Growth Arena (MEGA) plate.

To observe how the bacterium *Escherichia coli* adapts to increasingly higher doses of antibiotics, the researchers infused serial sections of the dish with various doses of an antibiotic, ranging from no dose to a dose just above what the bacteria could survive, to a tenfold increase, culminating in a dose 1,000 times higher than the lowest concentration.

Over two weeks, a camera mounted on the ceiling above the dish took periodic snapshots that the researchers spliced into a time-lapsed montage. The result? A powerful visualization of bacterial evolution at work.

"We know quite a bit about the internal defense mechanisms bacteria use to evade antibiotics but we don't really know much about their physical movements across space as they adapt to survive in different environments," says study first author Michael Baym, an HMS research fellow in systems biology.

The researchers caution that their giant petri dish is not intended to perfectly mirror how bacteria adapt and thrive in the real world and in hospital settings, but it does mimic more closely the real-world environments bacteria encounter than traditional lab cultures. This is because, the researchers say, in bacterial evolution, space, size, and geography matter.

The researchers adapted the idea for an out-sized dish from, of all places, Hollywood. Senior study investigator Roy Kishony, of HMS and Technion, had seen a digital billboard advertising the 2011 film *Contagion*, the tale of a deadly viral pandemic. The billboard featured a giant lab dish with hordes of painted, glowing microbes creeping across a dark backdrop to spell out the movie's title.

"This project was fun and joyful throughout," Kishony says. "Seeing the bacteria spread for the first time was a thrill. Our MEGA-plate takes complex, often obscure, concepts in evolution, such as mutation selection, lineages, parallel evolution, and clonal interference, and provides a visual seeing-is-believing demonstration of these otherwise vague ideas. It's also a powerful illustration of how easy it is for bacteria to become resistant to antibiotics."

"What we saw suggests that evolution is not always led by the most resistant mutants," Baym says. "Sometimes it favors the first to get there. The strongest mutants are, in fact, often moving behind more vulnerable strains. Who gets there first may be predicated on proximity rather than mutation strength."

—Ekaterina Pesheva

MICHAEL BAYM

Good Intentions

Nearly half of pediatric clinical trials go unfinished or unpublished

CLINICAL TRIALS IN CHILDREN commonly go either uncompleted or unpublished, according to a comprehensive study from HMS researchers at Boston Children's Hospital. This perplexing news comes forward at the same time as recent legislation encouraging clinical trials in children, including the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

According to the study, published online August 4 in *Pediatrics*, 19 percent of trials were stopped early and results from 30 percent of completed trials remained unpublished in the medical literature several years later.

"We feel there is a lot of inefficiency and waste that could be addressed," says senior investigator Florence Bourgeois, an HMS assistant professor of pediatrics at Boston Children's.

Adds co-author Natalie Pica, an HMS clinical fellow in pediatrics at Boston Children's, "Our findings are in line with previously published studies focusing on adult trials, which may speak to how commonplace discontinuation and nonpublication are in medical research in general."

The researchers found that more than 8,000 children were enrolled in trials that were never completed and more than 69,000 children were enrolled in completed trials that were never published.

"We need to make sure that when children participate in clinical trials, their efforts are contributing to broader scientific knowledge," says Pica.

Pica and Bourgeois tracked 559 randomized, controlled pediatric trials registered on ClinicalTrials.gov from 2008 to 2010 and whose status (completed or discontinued) was confirmed as final after December 31, 2012. They then searched for related peer-reviewed publications through September 1, 2015. When no publication could be found, they emailed study investigators and sponsors.

Overall, trials sponsored by industry were more likely to be completed than trials sponsored by academic institutions, the investigators found. However, completed trials sponsored by industry were less likely to be published than trials sponsored by academia and government. These findings are similar to those seen for clinical trials in adults.

—Nancy Fliesler

No Beans About It

Antibiotic gel may offer relief for ear infections

A SINGLE-APPLICATION bioengineered gel squirted into the ear canal could deliver a full course of antibiotic therapy for middle-ear infections and make treatment of this common childhood illness much easier and safer, according to an animal study conducted by HMS researchers at Boston Children's Hospital and Massachusetts Eye and Ear. The findings appeared September 14 in *Science Translational Medicine*.

Middle-ear infection, or otitis media, prompts 12 to 16 million clinical visits per year in this country alone and is the number one reason for pediatric antibiotic prescriptions. But, as parents know, getting young children to take oral antibiotics several times daily for 7 to 10 days is daunting.

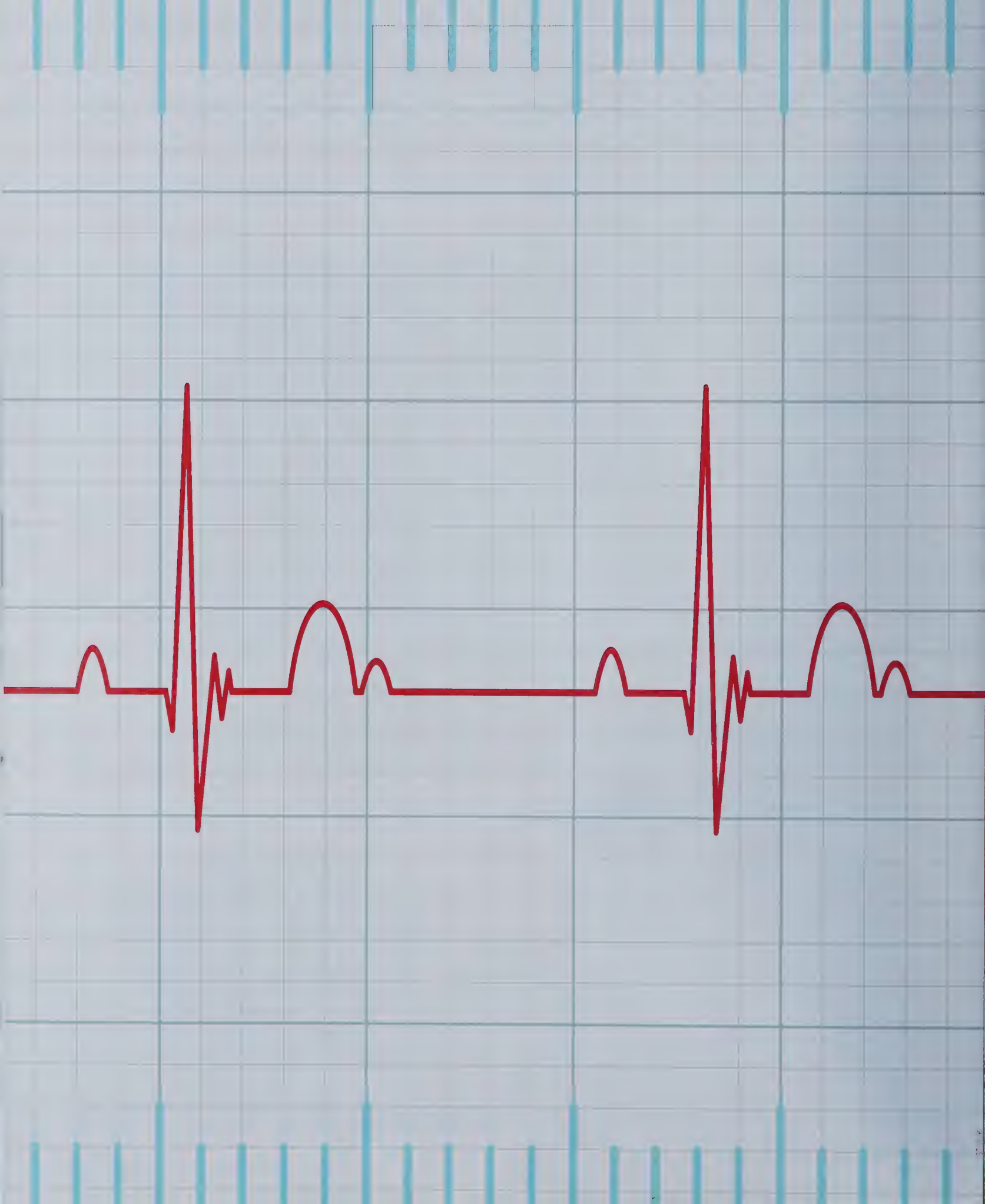
Children also seem to get better within a few days, so parents often stop treatment too soon. Incomplete treatment and frequent recurrence of otitis media—40 percent of children have four or more episodes—encourage the development of drug-resistant infections. And because high doses are needed to get enough antibiotic to the ear, side effects like diarrhea, rashes, and oral thrush are common.

The gel was tested in chinchillas, rodents that have an ear structure similar to that of humans. Further tests will be needed to determine safety and efficacy in humans.

Squirted into the ear canal, the gel quickly hardens and stays in place while it gradually dispenses antibiotics across the eardrum into the middle ear.

The bioengineered gel gets drugs past the eardrum barrier with the help of chemical permeation enhancers (CPEs), compounds that are FDA-approved for other uses. The CPEs, which are structurally similar to the lipids in the eardrum's outermost layer, insert themselves into the membrane and open molecular pores that allow the antibiotics to seep through. *—Nancy Fliesler*

Middle ear anatomy



Is it time to reconsider the dead-donor rule?

a fine line

He was in the middle of a court case when he clutched his head and collapsed. Massive cerebral hemorrhage. The 45-year-old lawyer was rushed to Boston's Brigham and Women's Hospital. ■ To the physicians in the intensive care unit, it became clear that the patient had an irrecoverable brain injury; he would never wake up. After six days, his wife and two teenage children made the heartbreaking decision to withdraw life support. At least, they thought, they would be able to honor their husband's and father's wish to be an organ donor. ■ It wasn't, however, so straightforward.

by Stephanie Dutchen

Because of a nationally agreed-upon principle called the dead-donor rule, the transplant surgeons wouldn't be able to remove vital organs unless the patient was dead. Since he didn't meet all the criteria for one definition of death—brain death—the family's only option was to have his organs donated after cardiac death, when his heart stopped beating.

The patient was wheeled to an operating room and his ventilator disconnected. Then the wait began: If the heart stopped within an hour, and didn't spontaneously restart within a few minutes after stopping, the attending physician would declare death, and then transplant surgeons would come in and retrieve the organs that remained usable. Longer than that, however, and poor circulation would render the vital organs unsalvageable.

Thirty minutes passed: the chance to rescue a transplantable liver evaporated.

His heart struggled but still beat.

Forty-five minutes elapsed. Sixty. The kidneys and pancreas were no longer usable.

After 80 minutes, the team gave up hope of rescuing even the hardiest organs. The patient began the trip back to the ICU.

His heart stopped in the elevator.

"The wife was very upset. The clinicians were upset," recalls Thomas Cochrane, an HMS assistant professor of neurology at Brigham and Women's who spoke with the family after the incident. "She didn't understand why her husband's organs couldn't have been taken out before his heart stopped. Nobody benefited from letting things happen that way."

Half a century after solid organ transplantation became a reality, the dead-donor rule remains a hotly contested topic in the transplant community. The rule is an ethical standard, not a law. Some of its most prominent critics are based in the Harvard medical community. So are some of its staunchest defenders.

Thomas Cochrane

Push, Pull

Proponents of sustaining the dead-donor rule emphasize that it strengthens public trust in the organ transplantation system by assuring potential donors and their loved ones that organs will not be removed before a person is declared dead. The rule fulfills the responsibility of physicians and surgeons to ensure that the removal of the heart or lungs, for example, does not cause a patient's death. Perhaps most importantly, it underscores the foundational medical doctrine: Do no harm.

"In my estimation, on the scale from trust to expediency, I'm prioritizing trust," says Francis Delmonico, an HMS professor of surgery, part-time, at Massachusetts General Hospital and chief medical officer of the New England Organ Bank.

Detractors point out that harm is already occurring. Dying patients who don't fit the stringent requirements of the dead-donor rule and who want to donate their vital organs are prevented from doing so. Loved ones experience a double loss, a death without the opportunity to save others. At times, the quest to satisfy the rule unsettles practitioners, dissuades patients who want to donate, and compromises the quality of the transplantable organs.

"From the donor's perspective, the dead-donor rule can interfere with your legitimate moral and medical goals," says Cochrane,

who is also director of neuroethics at the HMS Center for Bioethics.

A vocal minority led by Robert Truog, director of the HMS Center for Bioethics and the Frances Glessner Lee Professor of Medical Ethics, Anaesthesia, and Pediatrics at HMS and Boston Children's Hospital, thinks the medical establishment should do away with the dead-donor rule and instead focus on minimizing harm and maximizing consent.

"With a more straightforward approach," says Truog, "we could allow people to die in the way they want to die while still being able to fulfill their request to donate."

Even though advanced surgical techniques have made transplantations more successful, supplies of internal organs are notoriously limited. Abolishing the dead-donor rule would seem to open one avenue to more donations, but Cochrane and Truog emphasize that the driving factors behind reevaluation are not organ shortages but rather the desire to do right by patients and practitioners and confront changing definitions of death.

"The price society is paying for insisting that doctors continue to follow the dead-donor rule is increasingly high," says Daniel Wikler, the Mary B. Saltonstall Professor of Ethics and Population Health at the Harvard T.H. Chan School of Public Health.

The Birth of Death

Some say the debate began percolating in the late 1960s, when an HMS ad hoc committee chaired by Henry Beecher '32, then an HMS professor of anesthesiology, advocated expanding the *Black's Law Dictionary*'s definition of death to include what French physicians termed *coma dépassé* and the Beecher committee called brain death; that is, complete and irreversible loss of brain function.

The rule fulfills the responsibility of physicians and surgeons to ensure that the removal of the heart or lungs, for example, does not cause a patient's death.


Francis Delmonico

"An organ, brain or other, that no longer functions and has no possibility of functioning again is for all practical purposes dead," the committee members wrote in *JAMA* in 1968. They then outlined the criteria for determining whether a brain was permanently nonfunctional.

The Uniform Determination of Death Act, or UDDA, created in the early 1980s and adopted by all fifty states, reified the committee's decision by listing brain death as one of two manifestations of legal death, the other being the traditional definition of irreversible cessation of circulation and respiration.

Together, these reports established that with families' permission, doctors who withdrew life support from legally dead patients would not be committing murder or another illegal act. In doing so, the reports legitimized a pool of donation-eligible organs that were still being nourished and oxygenated.

Whether members of the Beecher or the UDDA committees were motivated by the desire to increase organ supply, and whether they stretched the definition of biological death to get there, remain points of contention.

A few practitioners, like Truog, say the committees could have been more nuanced. They could have asserted that while people with neither independent circulatory or respiratory function nor the hope of regaining consciousness are technically alive, it would be ethical to retrieve vital organs if consent had been given. For most in medicine, however, there is no doubt that both brain death and circulatory death are true death.

Wikler wrestled with these issues when he served on the presidential commission that drafted the UDDA. He had published a paper in which he argued that brain death shouldn't be considered death, but colleagues urged him to reconsider his position for the report or risk alarming the public.

He finally had to ask himself, "What's my highest priority? Is it to save lives, or is it to get the logic straight?" He decided, "It's to save lives."

The standard was upheld: Donor death is the only acceptable way to obtain vital organs.

"Maybe in the long run it would have been better to argue about the dead-donor rule than to argue about brain death," says Cochrane.


Robert Truog

Many Means to an End

Brain death isn't the only aspect of the dead-donor rule that raises practical and semantic quandaries.

Exact numbers haven't been gathered on organs lost to warm ischemia—damage sustained from little to no circulation while still at body temperature—but a 2014 paper in the *American Journal of Bioethics* estimated that waiting for cardiac arrest after removal of life support, and then waiting a few minutes more, eliminates 2,200 organs from the donor pool each year. Another 6,700 organs may be lost annually while waiting for donors with severe brain injuries to progress to brain death.

The volume of compromised or unusable organs combined with a lack of conclusive evidence about the minimum amount of time after which a nonbeating heart is unlikely to restart on its own have prompted some institutions to trim the waiting period for donation after cardiac death. Wait time after cardiac arrest shrank from 2 minutes to 75 seconds at one Colorado hospital, for example.

Those in favor of eliminating the dead-donor rule emphasize that a replacement system must be based on extraordinarily high standards of consent.

In addition, since some hearts retrieved after so-called cardiac death can be transplanted and restarted, debates churn about whether the donor was really dead.

In small pockets around the country, "imminent death" donation has gained a foothold. Under this protocol, surgeons retrieve a patient's kidney or liver lobe with consent, allow a few days of "recovery," then cease life support. The sequence serves to prove the organ removal didn't kill the patient.

These and other variations "have made a lot of people queasy," says Truog.

Truog helped craft the protocol for donation after cardiac death at Boston Children's and is among those who dislike workarounds. "We are honoring the dead-donor rule in the breach," he says. Instead, he and colleagues advocate for simplicity and transparency.

Public's Pulse

Those in favor of eliminating the dead-donor rule emphasize that a replacement system must be based on extraordinarily high standards of consent and a commitment to ensuring that patients aren't harmed. Rigorous medical, legal, and ethical guidelines would be essential to easing slippery-slope concerns.

"With proper safeguards, no patient will die from vital organ donation who would not otherwise die as a result of the withdrawal of life support," Truog co-wrote in the *New England Journal of Medicine* in 2008.

Responsibly revised rules, they say, would help protect vulnerable populations, such as people with dementia and mental illness, and disallow people from volunteering for suicide by donation.

Even with these proposed safeguards, fear of public condemnation makes those on both sides of the debate reluctant to speak up. Voicing the possibility of taking people's organs before they're dead, let alone suggesting that it may already be happening, could shatter the fragile trust the transplantation community has earned since the 1960s.

"We don't want that to happen," says Wikler. "Organ transplantation is one of the reasons to be grateful we have modern medicine."

But would that trust really shatter? Cautious optimists like Truog and Cochrane point to clinical experiences where family members refer to brain-dead loved ones as being "kept alive" on ventilators yet have no qualms about donating their organs.

A few studies have attempted to gauge public opinion. In a 2014 survey of 1,000 U.S. residents reported in the *Journal of Medical Ethics*, 71 percent of respondents said

JOHN SOARES (SPREAD)


Daniel Wikler

it should be legal to donate the organs of patients in irreversible coma even though donation would cause their deaths; 67 percent said they would want to donate in such a situation. A 2016 survey in the *Journal of Medicine and Philosophy*, however, found that the public is "increasingly wary" of conflicts between organ donation and determination of death.

Biding Time?

Forty years ago, withdrawing life support from hopeless cases was considered the proximate cause of patients' deaths. Gradually, laws changed to reflect medical community and public agreement that patients' preexisting conditions were what caused their deaths. The same transformation could occur regarding the removal of vital organs.

If organ banks and policymakers remain conservative in their approaches to the removal of vital organs, it's because medical practice needs to change slowly, waiting for professional and societal tides to turn.

While they wait for this possibility, critics of the dead-donor rule may find themselves thinking one thing and practicing another.

"I have to be somewhat split-brained," says Truog. "As an ICU physician, I need to practice in a way that respects the status quo. In conversations with colleagues and when I teach, I talk about it in a different way."

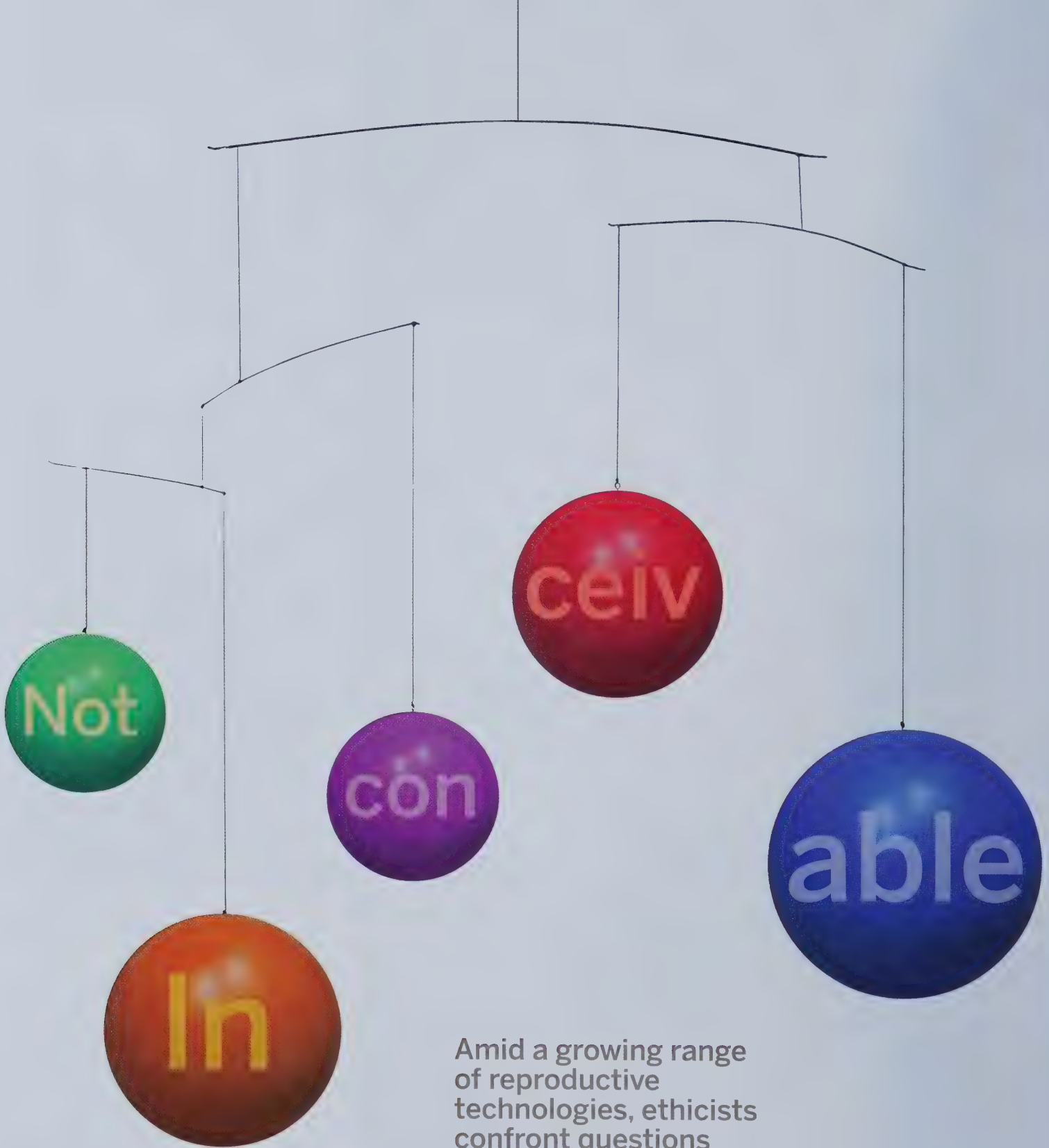
Perhaps the dead-donor rule, however fraught, needs to hold for only another ten or twenty years, until one research avenue or another leads to an alternative organ supply.

"When organs come entirely from pigs, we're no longer going to need a diagnosis called 'brain death,'" says Truog. "Maybe we should just wait."

But holding out for a technological deus ex machina doesn't satisfy everyone. "I hope that happens, because everybody will benefit," says Cochrane, "and I also don't want it to happen, because this ethical argument needs to be sorted out on its merits."

If one day, doctors, surgeons, patients, families, lawyers, policymakers, ethicists, and others agree that overhauling the dead-donor rule would do more good than upholding it, there would be reason for both celebration and worry. The battle over definitions and greater patient autonomy would be won, but then the hard work of implementation would begin. ■

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



Amid a growing range of reproductive technologies, ethicists confront questions arising from access and application

by Elizabeth Cooney

Louise King shakes her head as she considers her title at the HMS Center for Bioethics: director of reproductive ethics. Who, she asks, could presume to direct such a multidimensional field? ■ A recent morning at Beth Israel Deaconess Medical Center offers a glimpse into one of the field's dimensions as King, who also is an HMS assistant professor of obstetrics, gynecology, and reproductive biology at Beth Israel Deaconess, makes her way to an ethics committee discussion about a particular couple's request. As the parents of a seriously ill child, the couple hoped for assistance in selecting an embryo that would become the best match for their child, who, barring a bone marrow transplant from a compatible donor, had a poor prognosis. In short, they wanted help conceiving a "savior sibling."


Louise King

The technology that could help them is one of several collectively referred to as assisted reproductive technologies, ART for short. And while ART can make babies, it cannot say who should have them.

Neither can ethics committees, which helps explain King's wonderment at all that her title represents. Bioethicists and clinicians like King and her colleagues see themselves as educators, explaining the medical consequences of certain decisions and providing a prism through which these learners and teachers try to refract the future.

Room for More

Perhaps the most recognized ART procedure is in vitro fertilization, or IVF, but technologies such as cryopreservation and preimplantation genetic diagnosis are also available. In general, these technologies are used to assist human reproduction in individuals who, for one reason or another, have not been able to conceive by other means, including other medical and surgical options. It's not without failure, but ART can help the 15 to 20 percent of heterosexual couples who are infertile achieve a viable pregnancy.

The range of available technologies also means that more people can now become parents. IVF, for example, can help gay or transgender couples have children: Egg and sperm can be combined in a lab dish and implanted later in one parent or in a gestational surrogate.

The availability of ART poses the question of whether everyone has a right to medical interventions to increase their chances of conceiving.

Rosemary Reiss

Cryopreservation, another type of ART, can preserve fertility for cancer patients or for people not yet ready to start a pregnancy. Preimplantation genetic diagnosis can be used to diagnose disorders in embryos or predict the risk of disease in adulthood, while embryo selection technology can allow parents to choose one embryo over another. The latter is employed in savior sibling situations.

Balancing Act

Ever since Louise Joy Brown came into the world on July 25, 1978, bringing with her the term "test-tube baby," people have been troubled by the role of technology in reproduction. Members of the clergy, for instance, have been concerned about humans playing God, and, together with nonclerics, have feared—and still fear—the use of these new tools to create so-called designer babies.

As the number of children born using ART grew, however, so did demand for the technologies. Swelling demand brought waves of ethical questions, each one incrementally advancing the discussion.

One example of such an advance involved parenthood for gay couples. Thirty years ago, hospital committees debated whether to help gay couples have children. Such a case would not reach an ethics committee today, as both social norms and clinical policies have evolved.

Savior siblings, too, have gained in acceptance. Fears for the child conceived as a donor have been allayed as families with such siblings have found the experience to be beneficial.

Cases that do get a hearing by committee or a consultation with a bioethicist are sometimes brought up for discussion by clinicians who want to explore their own discomfort with going forward. King calls it the "ick" factor in ethics: What makes you uneasy demands to be examined.

Once providers enter the equation, they become moral agents, bringing their own principles and beliefs into the picture. Should they implant an embryo with a risk of disability when patients and clinicians disagree on what defines disability? What about gender selection?

Some ethicists say one could argue there is no more reason to question the suitability of a parent when ART is involved than to evaluate it when people have children the "natural" way. If parents considering a sibling for a sick child in need of a transplant would

have had a child anyway, what is the harm in using ART to select the best match?

In weighing such questions, bioethicists lean on four pillars: autonomy, justice, beneficence, and nonmaleficence. These terms frame as essential the right to choose, the importance of treating all people fairly, the hope of doing good, and the prevention of doing harm.

"There are balances in every choice we make, and the enhancement of a patient's autonomy is done by affording them a full understanding of everything that's being offered to them," King says. "I'm not an arbitrator. I'm mediating a discussion so that everybody can exercise their own autonomy."

The Rights Direction

Future children factor into the discussions as well. In the savior sibling scenario, King worries about expectations placed on the child conceived as a donor. Children also sit squarely in debates over what constitutes a disability or a disorder. Is deafness a disability? Is small stature?

Ethical principles do not mandate which people have a right to become parents, but the American Society for Reproductive Medicine does, or at least comes very close to doing so. An opinion piece on disparities in access to effective infertility treatments, published in November 2015 in *Fertility and Sterility*, one of the society's publications, states, "Creation of a family is a basic human right."

Rosemary Reiss, an HMS assistant professor of obstetrics, gynecology, and reproductive biology at Brigham and Women's Hospital, thinks creating a family is not a right in itself. Instead, she thinks that although people have a right to try to conceive, there can be no guarantee of a successful pregnancy. Society must protect everyone's right to choose to become parents; for example, the state or the medical community cannot force sterilization. But, she adds, this does not necessarily lead to the conclusion that society is obligated to devote unlimited resources to assisting infertile couples. She points out a distinction between the right to bear a child and the right to education for a child: In our society, the right to an education means there are laws that compel governments to provide education and that require parents to ensure their children receive that education.

"People may have a right to try to bear children," says Reiss. "The availability of ART poses the question of whether everyone has a right to medical interventions to increase their chances of success at conceiving. And, if they do, which interventions?"


Christine Mitchell

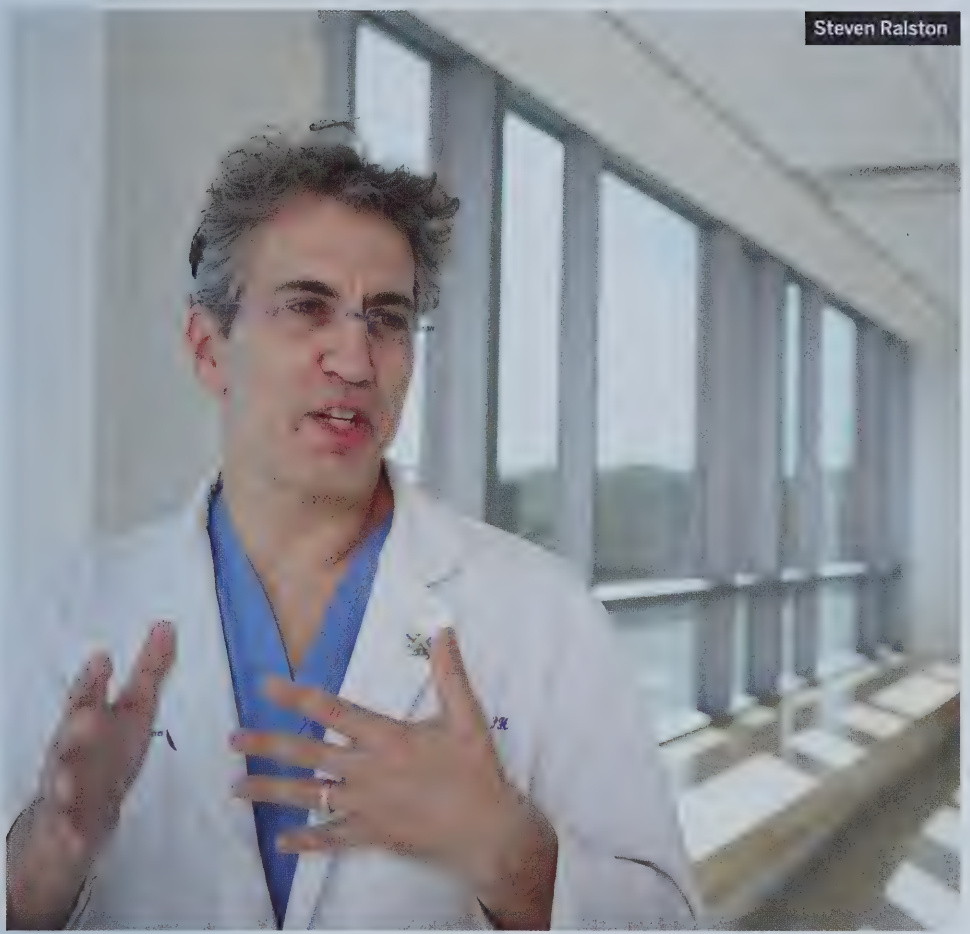
Public Constraints

In 2013, nearly 68,000 babies were born in the United States as a result of ART. Yet there is little regulation of the technologies in this nation compared to other countries, particularly those with national health services.

"It's pretty much the Wild West here, with unregulated opportunities to shop for someone who will help you become a parent," says Christine Mitchell, executive director of the HMS Center for Bioethics and a lecturer on global health and social medicine.

In such a market economy, insurance coverage depends on the state in which you live. In 2015, one cycle of in vitro fertilization, including medications, had a median price tag of $19,200. But only fifteen of fifty states mandate coverage for fertility care. Private insurance companies and Medicaid—and, of course, independent personal means—have become the arbiters of who can avail themselves of ART.

Ways of working within the narrow confines of coverage have led to such measures as double implantation. If a woman has exhausted coverage for cycles of egg implantation, she may ask a doctor to implant two embryos to increase her chances


Steven Ralston

of giving birth to one child. In Japan and the United Kingdom, only single-embryo implantation is allowed, a response to data showing poor outcomes for both mother and children as a result of pregnancies leading to multiple births.

The question of who has access to ART can arise far earlier in the process. Economic and social restrictions on ART can taunt those surrounded by a culture that says, in essence, "Go for it."

Yet, says King, if you look at who most often has access to IVF, "it's not simply people who are well-off and white. It's people who are well educated and understand what to seek out."

King thinks access to ART should be expanded, not only by increasing funding for ART services, but also by better educating primary care providers about infertility, its causes, and the importance of teaching young women from all walks of life about those causes.

"It is our duty as reproductive physicians and surgeons to ensure educational opportunities for our patients, regardless of their socioeconomic status," she says.

"What does it mean when we tell patients that they might have a normal fetus that has this one characteristic that is not normal?"

Facing the Unknown

Educating people to the possibilities of assisted reproduction also means educating them to the risks.

No one likes to dash hopes when genetic test results reveal potential problems, says Reiss. No one likes to say no.

"You'd like to make it possible, so you say, here are the risks. Many disorders have a spectrum of severity and not all tests are as accurate as one might hope."

Preimplantation genetic tests now look for hundreds of abnormalities, rather than just a handful of well-known conditions, such as Down syndrome. Predicting the severity of a disorder can be challenging, and the way in which providers convey that information and its limits—upbeat or grave—can affect how the prospective parents receive it, says Steven Ralston, an HMS associate professor of obstetrics, gynecology, and reproductive biology at Beth Israel Deaconess.

Providers feel an ethical obligation to present as much information as they can, as clearly as they can, even when they do not have all the answers.

"What does it mean when we tell patients that they might have a normal fetus that has this one characteristic that is not normal?" Ralston asks. "Does that become the overriding characteristic that they then are making decisions about, rather than everything else that might be normal—the Down syndrome, the spina bifida, the disability—rather than the joys a baby might bring to their lives?"

Freeze Frame

Age, too, is often a barrier to access, although how much of a barrier varies clinic to clinic, with age 50 usually the cutoff for providing ART services to women seeking to bear a child.

A different perspective on age and assisted reproduction has arisen recently following the offers by Silicon Valley companies to provide female employees a new health benefit: coverage for the cost of cryopreserving their eggs. The benefit triggered concerns about encouraging women to postpone parenthood in deference to their careers or the demands of corporate culture. The ethical question involved having an employer become an actor in a private decision.

Concerns over decisions about reproduction ultimately do not vary from those for any medical question: what could go wrong and who might be hurt. When there is no case history to consult, bioethicists look at the pursuit of happiness as an acceptable point from which to begin framing such decisions, until, of course, the happiness of one bumps against the well-being of another.

It's likely the waters of these decisions will always remain murky—the reasons individuals or couples may have for wanting or needing help with achieving, postponing, or directing a pregnancy will always vary as much as the individuals asking. While ethicists may not have the answers, they are trained and prepared to help patients and physicians wrestle through questions of conception. ■

Elizabeth Cooney is a science writer in the HMS Office of Communications and External Relations.

Japanese Red Cross taking care of enemy soldiers near the Amur River
1904
Lithograph

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Can doctors who deliver medical care following disasters shift their thinking from what's good for the one to what's good for the many?

In Short Supply

by Elizabeth Dougherty

When a calamity strikes and tens of thousands of people need help, the first impulse is to cry "All hands on deck!" ■ Not so fast, say experts in disaster relief. ■ "It was always thought that in a disaster there wouldn't be time to measure the quality of the aid, and no real reason to do so," says Michael VanRooyen, an HMS professor of emergency medicine, head of the Department of Emergency Medicine at Brigham and Women's Hospital, and director of the Harvard Humanitarian Initiative at Harvard University. "We assumed that any care is good care. But we now know that's not the case." ■ When providing medical care in disasters, health care providers must make on-the-spot decisions about who should receive care and how much, and they must do so with the knowledge that resources are limited in every conceivable way.

To help physicians navigate these decisions, experts in disaster care have begun to systematize triage, resource management, and training. The aim: to professionalize the delivery of disaster medical care by teaching humanitarian professionals how to make evidence-based decisions that draw on their deep knowledge and past experience. Such a change, say many, could also make the delivery of such care more needs-based and more ethical.

Evolutionary Behavior

Those who have participated in humanitarian aid know all too well what can go wrong when the response is uncoordinated and doctors and nurses arrive on the scene without having been trained in disaster response.

Poor triage of acute wounds, for example, can lead to inappropriate medical care and years of suffering for the patient. This particular complication cascade revealed itself after the 2010 earthquake in Haiti. Although triage decisions addressed patients' immediate needs, experts say they also produced hundreds of thousands of trauma cases that required postoperative care and rehabilitation that the infrastructure-strapped country still struggles to provide. Another example was the aid response to the 2015 earthquake in Nepal. That response became so unwieldy the country had to turn aid workers away, says Jennifer Leaning, an HMS associate professor of emergency medicine and the François-Xavier Bagnoud Professor of the Practice of Health and Human Rights at the Harvard T.H. Chan School of Public Health. The workers were sapping resources that were limited, including such basics as shelter, food, and water.

The realization that more is not always better hits at the heart of the ethics of giving care in a disaster.

"Doctors in the United States are conditioned to caring for individual patients and working to achieve spectacular outcomes," says Leaning, who also directs the FXB Center for Health and Human Rights at the Harvard Chan School. "They also tend to hew to the thinking that more individual attention is better."

"Disaster is a time of altered standards of care," says ethicist Nir Eyal, an associate professor of global health and population at the Harvard Chan School. "The attention must shift to population-level outcomes."

This shift to a population-based approach to delivery of health care is difficult for many Western-trained doctors and nurses, says Leaning, for it differs from the personalized care they are accustomed to providing. The trouble, she adds, begins with the first medical encounter when the health provider must attend to an individual's needs but must do so in a manner that allows for the ongoing delivery of care to a larger group or the entire population. The health care providers must deploy limited, often dwindling, resources to deliver the greatest good to the greatest number of people.

ASSOCIATED PRESS

"Keeping your focus on both the individual and the population at the same time is disorienting—and troubling," says Leaning.

What disaster-relief scientists such as Leaning and VanRooyen are finding is that health care professionals cannot make this conceptual shift on their own. They need guidelines, best practices, and training—the

HOME VISIT: Volunteer medics dispensed care to injured and displaced Nepalese villagers following the 2015 earthquake.

Disaster care is becoming a standards-based profession, complete with recognized guidelines and best practices.

very tools that would result from a systematization of disaster medical care and its protocols. This systematization is, in fact, happening, albeit slowly. Disaster care is becoming a standards-based profession, complete with recognized guidelines and best practices that are being crafted by the World Health Organization and other international aid bodies.

"This transition constitutes a remarkable innovation," says Leaning. "We need to be moving toward a self-correcting ethical system of professionalism."

Up Close

In 1996 when Mary Ann Hopkins '92 headed for the U.S. office of Médecins Sans Frontières, the international humanitarian-aid organization had yet to receive the Nobel Peace Prize. In fact, its New York office employed just a handful of people. Hopkins had happened upon one of its brochures during her surgical residency in New York City and, having previously served as a foreign aid worker, decided to sign up.

They sent her to Sri Lanka, which was in the middle of a bloody, protracted civil war.

Hopkins, now an associate professor of surgery and the director for global health initiatives at the NYU Langone Medical Center, had requested an assignment outside of the active war zone. But, as she traveled from New York to eastern Sri Lanka, the conflict spread. A few weeks after she arrived at her post, the front lines came to her.

"My constant concern was that I would have too many casualties arrive at one time," says Hopkins.

Fundamentally, aid workers are guided by the universal principles of maintaining neutrality in conflicts and providing nondiscriminatory care. Hopkins and her colleagues cared for both the victims and the perpetrators of the violence without hesitation. Hopkins's father, Robert West Hopkins '47, adhered to the same principles during the Korean War, when, as a lieutenant in the U.S. Navy, he served as a surgeon on the USS *Repose*. "When he talked about his war experiences, he talked about the need for impartiality," Hopkins says. " 'You always treat everybody.' "

Yet limited resources in a disaster make it impossible to treat everybody. Medical aid workers must find a way, second by second, to do the most good for those who are suffering even if it means choosing to limit care to those who cannot be saved.

Such decisions require difficult choices. They also require practice.

Work to Rule

In medicine, triage, derived from the French *trier*, to sort, applies to initial assessments of acute patient needs, to follow-up assessments, and to decisions on the allocation of supplies and expertise.

The fundamental coding in acute triage is similar whether a patient is coming to a hospital's emergency department or to the medical intake area in a disaster-relief zone. The degree of patients' need for medical care is identified using a system of color codes. Black, for example, indicates patients who are unlikely to survive and should not receive treatment. Those coded red need, and receive, immediate intervention, while yellow indicates a patient whose needs are less urgent. Green indicates no care is required.

In a disaster, however, far fewer people can be helped than could be under less-trying circumstances. To make tough and troubling decisions about who will receive assistance and who will be left unattended, regardless of medical need, health care providers must train. "Decisions about life and death or medical futility are rare," says VanRooyen, "but when they are necessary, they are distracting and difficult. So we drill."

During Hopkins's years of service as an emergency surgeon in conflict zones in Burundi, the Republic of the Congo, the Central African Republic, and elsewhere, she encountered patients she could not save, in some cases because the available equipment wasn't sophisticated enough for her to perform the needed surgeries.

"You will not always be able to do what you think you should do," says Hopkins. "That fact has persisted throughout every mission."

A World View

While health care providers are working to establish clear triage guidelines, an increasing need for global disaster aid is propelling efforts to systematize post-disaster medical care. According to a 2014 report from the United Nations Office for the Coordination of Humanitarian Affairs, the number of people needing humanitarian assistance has doubled in the past decade, and the numbers continue to rise.

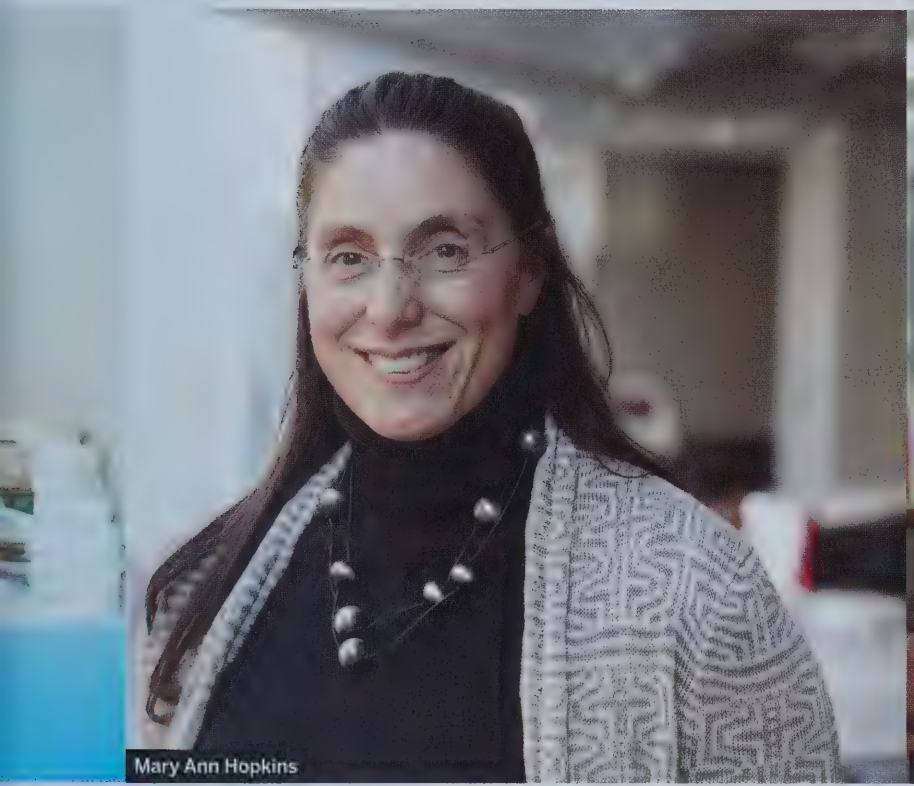
"The scale of morbidity and mortality has risen sharply," says VanRooyen.

One reason for the increase, according to the UN report, is climate change, which is increasing the incidence and intensity of floods, hurricanes, droughts, heat waves, and other severe weather events. Between now and 2050, the report projects, climate change could displace a billion people. There also is an uptick in population movement to urban centers, which can have poor infrastructure and insufficient and unsafe housing. In addition, there are the pressing needs of ongoing political conflicts, such as the civil war in Syria.

The report also says that crisis relief funding needs have increased sixfold in the past decade. Because of this need, the ability to provide ethical and beneficial disaster care hinges not only on decisions made during acute care triage, but also on those made during the triage of limited resources, which range from the availability of surgeons like Hopkins to the use of medical supplies including painkillers, oxygen, antibiotics, and vaccines.

"Decisions about life and death or medical futility are rare, but when they are necessary, they are distracting and difficult. So we drill."

According to VanRooyen, vaccination against measles provides a clear example of triaging resources for the public's health. Migrating populations need vaccinations to stay healthy. But, he says, "Immunizations for


Mary Ann Hopkins


Nir Eyal

mumps, rubella, tetanus, and polio can wait. Measles will kill a third of the children in three weeks if they aren't vaccinated."

Not all resource-use decisions are so clear-cut. Water, for instance, must be provided to individuals in refugee camps, but only potable water is made available; supplying non-potable water as well adds risk. Aid organizations currently aim to supply the standard three liters of drinkable water per person per day. It's a woefully small amount considering the ration must be used for cleaning cooking utensils, food preparation, personal hygiene, and drinking.

But is three liters the right amount? No one knows; it has never been rigorously studied.

"The amount comes from early work—in Biafra in the 1960s and along the Thai-Cambodian border in the 1980s," says Leaning.

It is neither feasible nor ethical, she adds, to run a randomized clinical trial at a refugee camp to test whether refugees receiving two-and-a-half liters of water fare any differently from those receiving three.

As work continues at the organizational level to systematize disaster care, significant time is spent in the field thinking of ways to run studies. When she conducts training sessions in disaster relief, Leaning uses historical experience and anecdote as evidence for practice.

"It's a distilled understanding," she says, "a sort of word-of-mouth apprenticeship."

Experts develop and incorporate best practices and the practices are folded into existing guidelines in publications such as the *Sphere Handbook: Humanitarian Charter and Minimal Standards for Humanitarian Response*. The book, published by the Sphere Project, which was developed by seasoned humanitarian responders from various aid organizations, sets forth standards for water and food management and health care responses and serves as a guide for the humanitarian community.

"It's a very informative book and has increasingly become more ethics-based and focused on human rights and key principles," says Leaning.

As of 2015, professional development for medical aid workers has included the option for global certification. The Emergency Medical Team program that is administered by WHO focuses on training medical personnel to provide integrated care in a disaster. Because of the program, WHO can now provide specific countries with rosters of qualified providers—a registry of trained professionals who have made a commitment to provide disaster care and who work to continually improve their skills. The ability to tap a cadre of skilled individuals and teams committed to disaster relief stands in sharp contrast to the traditional open calls for aid.

"The days of disaster excitement have to be over," says Leaning. "We need dependable professionals who train and retrain, so that aid organizations can be assured that they are bringing in seasoned professionals to be part of the response."

The Bigger Picture

While professionalizing disaster care promises to improve humanitarian aid efforts, there is a danger that too much systematization could lead to mechanistic care. Procedures and processes could become barriers to truly seeing the humans in jeopardy.

"If you are just doing the clinical and operational triage, you are going to outrage people and deny their dignity," says Leaning. "When we talk about doing the greatest good for the greatest number in public health and medical care, the 'good' is life. We're not distributing money. We're distributing access to living." ■

Elizabeth Dougherty is a Massachusetts-based science writer.

MORALITY TALES

THERE'S MORE THAN A BIT OF SOUL-SEARCHING NEEDED WHEN PHYSICIANS BRING PATIENTS' STORIES OUT OF THE CLINIC AND ONTO THE PAGE

BY PERRI KLASS

We physicians know that medicine is full of stories.

They keep us going, keep us coming back, sometimes keep us up at night. From your earliest clinical experiences as a medical student, you start building your private stock of stories: comedies and tragedies, dramas and shockers, quests and sagas and mysteries. Our training includes learning to construct narrative using the medical tools of the presentation and the write-up. Nowadays, in the interest of medical humanism, students and residents are often asked to construct "reflective narratives" in which they take time to consider and describe some of the complex aspects of medical stories that get left out of the formalisms of the medical record. ■ Given all that richness of incident, it's not surprising that many doctors think about taking the incidents of the exam room or the operating room or the hospital ward out into public discourse and telling the world. But when we do that, ethical questions instantly crowd in, from the immediate issues of confidentiality to the overarching question of who owns the story and who has the right to tell it. ■ I've been writing and publishing stories about my clinical experiences since my first year of medical school, which means I have accumulated more than 30 years' experience in weighing the ethical, professional, and literary rights and wrongs of what you tell and what you don't. I think that gives me a certain authority to say on behalf of doctor-writers: We're all making it up as we go along. Certainly, that's what I'm doing. ■ Jerome Groopman, the HMS Dina and Raphael Recanati Professor of Medicine at Beth Israel Deaconess Medical Center, has been writing stories about patients and doctors for the *New Yorker* for almost two decades. The question of who owns, or should tell, the story, he says, does not have a simple answer. ■ "I think it's a real issue," he says. "It's something that has to be thought about with real sensitivity because of the power imbalance and the sense that patients want to please their doctor or want to give their doctor something." ■ Once a doctor becomes known as a writer, the interaction gets even more complex. "I've had patients say to me, 'Well, I hope I'm not going to be a chapter in one of your books,'" Groopman says. "I say 'Absolutely not. I'm a doctor first and foremost.'"

"I think you hurt your credibility if you put one

A physician-author may also encounter patients who hope their stories will be told, and who put the doctor in the thankless, editor-like position of needing to find a polite way to say, "Thank you so much, but this isn't right for publication."

Just the Facts, Ma'am

As the editor of the Well section in the *New York Times*, Tara Parker-Pope regularly receives and reviews narratives sent in by physicians. About six years ago, the *Times* published one such piece in which the patient, who was suffering from depression, was quoted as saying she was stressed about taking part in a regatta on the Schuylkill River. Readers wrote in to suggest that they might be able to identify the woman: The rowing community is relatively small and close. When Parker-Pope questioned the physician-author, it turned out that rowing was an invented detail—the patient was an athlete, but in another sport altogether.

"Ever since then," Parker-Pope reported in an email, "we always double-check when doctors write for us, because we know the culture of the medical writing community allows for fabrication of details to protect patient identities. We don't ever allow it."

Arthur Caplan, the head of the Division of Bioethics at NYU Langone Medical Center, points out that journalism rests on a framework that holds that the absolute truth—in detail as well as essence—is an ethical good.

"Journalism wants the real identities," he says. "Journalism loves reality—it's a strong strong ethos."

The thing about stories is that God is in the details. It's the characters, the human touches, and the actual words that people say that make clinical encounters so complicated and compelling, so memorable and even haunting.

So what do doctors do with those details when they want to tell a story from clinic?

When I started writing about medicine, I went editor by editor in terms of how I handled identifying details. Most often, I suppressed them, but sometimes in magazines, which were willing to publish a disclaimer notice that details had been changed, I altered patients' ages or genders.

I became increasingly uncomfortable with such alterations. I now teach in a journalism department and have come to believe in the journalistic standard— truth is truth, anything else is fiction. You suppress details, to keep people anonymous and unrecognizable, but you don't alter them. And in fact, as Parker-Pope's story illustrates, when you change details to conceal someone's identity, you may in fact be identifying some real person who happens to fit your invented profile.

"I think you hurt your credibility if you put one untruth in your story," Parker-Pope says, "one small white lie, you impugn the credibility of your entire story."

Teaching Points

A few years ago, somebody challenged me on the ethics of a story I had published, a true story about supervising the initial patient encounters of a small group of first-year medical students.

I had arranged for the students to interview the grandmother of a child who had spent a long time in the PICU after a bad accident. The grandmother delivered a passionate and heartrending speech about her granddaughter. After she finished, I put my arm around her as I offered her a tissue. Later, one of the distinctly shaken medical students, a male, asked me whether it was okay to hug a patient.

I wrote about that situation, using the story to illustrate the emotional intensity of the patient encounter and the complex etiquette of comforting and listening, which the student's question evoked. When I read the published story to a largely medical audience, one of my listeners immediately brought up an ethical question: Had I asked permission before I published this story?

I smugly answered yes. Of course I had asked permission; I had spent a long time with the grandmother, asking if it would be okay for me to try and re-create some of her story in an essay about teaching and learning medicine, explaining that I would need to tell some of the story of what had happened to her granddaughter. Although I wouldn't use her name, if she and others, such as the doctors or nurses in the PICU, read it, they would know who the story was about. I told my interlocutor that the grandmother was happy to give me permission and that she had said she wished she could tell that story to medical students everywhere.

"No," said the woman in the audience, "I meant, did you get permission from the medical student?"

That had never occurred to me.

There are special rules that protect patients—in fact, there are laws that protect patients—but so long as I didn't use the names of medical students or residents (or colleagues or nurses), weren't my workplace stories fair game? I've thought more about this and I have to acknowledge that when there's a power imbalance, you have to apply different standards. I wouldn't write anything that in my judgement might make a student or a resident feel foolish or exposed, and I certainly would ask permission if I wanted to include any identifiable details. But would a student or a resident really feel free to say no?

I don't think, however, that medical students and residents are covered by the same protective mantle that shields patients. I think there's a need to acknowledge a potential power imbalance and to treat the young with care and respect and professionalism, but I don't think it's in the same ethical category as the doctor-patient dilemma.

Between Us

Can patients actually give consent freely when a doctor asks? There are several different ethical questions involved, starting with the power dynamic and the possibility that an inclination to say no will be complicated either by a sense of gratitude to the doctor or the worry that declining might hurt the relationship and the patient's future care.

There's also the question of whether people who agree to have their stories told

untruth in your story, one small white lie."

are fully aware of the possible ramifications. I once asked a patient in Boston if I could write about her interesting—and clearly identifiable—medical condition. She was technically an adult (19 or 20 years old). I told her I wanted to write about it for the *New York Times* and that I wouldn't use her name or any details about her family or her life. But, I pointed out that if people at the health center or the hospital read the article, they might know I was writing about her. She told me I could write about it—no problem—and could use her name; she didn't know anyone in New York, she said, so what did it matter? Needless to say, I was not particularly comfortable with that permission, and I didn't write the story.

"I think consent is possible as long as you warn people about the possible cost of their real name appearing," Caplan says, "and that their family might not be thrilled. You need to talk through what it means." He said that people have many reasons for wanting their stories to be told, from the noble, such as raising money for a cause they care about or hoping to help others through the same difficulties, to the less elevated, such as hoping for attention.

"I've seen it done well, and people haven't regretted it," he adds. "I think when you're dealing with vulnerable people—children, mentally impaired people, institutionalized people, people in the military—you hesitate."

Whose Story Is It?

We all learn medicine from the stories of our patients. We learn from our teachers' patients as well, through the stories that come down to us. For this reason, there is indeed a convention within the medical world that stories can be told, one exhibited in medical journal case reports and in patient stories in which details are redacted or, occasionally, altered.

"What we have generally done is leave things up to authors," says Debra Malina, the editor of the Perspective section in the *New England Journal of Medicine*. "My sense is the physician who's writing is the one with the relationship with the patient—that person has to be at peace with it." *NEJM* doesn't use real names when photos or x-rays of patients are published, and Malina thinks it's reasonable to publish the disclaimer with an essay that names have been changed.

"I think more of the time than not people get permission from the patient and change only details that seem irrelevant to the point," she says. "But we don't publish fiction; we make sure stories are true."

Malina gets most concerned, she says, when doctors submit articles that seem to be "pieces that are clearly for the glorification of the writer, and the patient is secondary." She worries that with more medical schools and residency programs encouraging reflective writing, there will be a risk that stories that are therapeutic for the physician may be written or published specifically because they are therapeutic for the physician.

"You have to think about whose needs you are serving and who you can hurt and in what way," she says.

Truth and Consequences

"Everyone makes up their own rules," Groopman says. "I see myself as a doctor first and a writer second. That's how I approach it."

A newspaper editor looks at doctors' stories as a journalist, responding to the ethic that Caplan identified: facts and truth are the highest standard. A medical journal editor looks at those stories in the context of the mission of the medical journal: to communicate important information that will improve medical knowledge and practice within the profession.

Here are my own guidelines. I'd like to promise you that I've always followed them, but I know that I've done my share of bobbing and weaving and probably will continue to do so for as long as I go on writing.

I have to be a doctor first and last. People are telling me what they tell me and showing me what they show me because I'm a doctor and that should guide all my behavior and responses.

Writing about patients has to meet the highest possible standards in terms of confidentiality, respect, and honor. Power differentials are real. If I do harm, even without intending it, I have committed a grave sin. Writing about students or residents also requires me to recognize similar ethical and professional strictures. But if there's no power differential and I'm writing about colleagues, I can offend people if I'm willing to deal with the consequences.

If I invent details, I am writing fiction and must identify it as such. Composite cases, teaching parables, and rich evocative narratives inspired by real events are all potentially worthy fictions, but they aren't true reported stories. It must be clear to the reader what is fiction, what is parable, what is teaching case.

Just because a patient story is important to me, or because writing it down is therapeutic for me, doesn't mean that story should be published. In fact, these are lousy reasons to take a story public.

I've gotten stricter with myself about protecting confidentiality, but also about not changing details, about separating fact from fiction, and even, I hope, about remembering that it isn't supposed to be all about me. But I'm sure I will go on making judgement calls that won't look so good a little further down the road, and I'm sure I'll go on worrying, which seems appropriate given the seriousness of the stories and the weight of responsibility to patients, readers, and even the medical profession.

"I've seen a lot of good that comes out of this," Groopman says. "I understand the risk of exploitation or misuse and so on, but I think there is a middle ground in the ethical dilemma between abusing your position as a doctor to write the story versus giving people an authentic and meaningful view of the lives of patients and the complexities that both patients and physicians confront." ■

Perri Klass '86 is a professor of journalism and pediatrics and director of the Arthur L. Carter Journalism Institute at New York University.


SCIENCE FOR PEOPLE
I PRACTICE SAFE SCIENCE
let's talk science
QUESTION EVERYTHING

Think Globally, Act Locally

Embracing the call for social responsibility takes many scientists into the public arena

by Ann Marie Menting

The science was elegant, powerful, and troubling, especially to those researchers deeply involved in the field. It could, the scientists acknowledged, revolutionize our understanding of fundamental biochemical processes in cells, propel the development of a new scientific discipline, and hold near limitless promise for medicine, industry, and agriculture. ■ It could also disrupt living beings in a most intimate way: It would change DNA. ■ Those involved in the work, gathered to discuss what they might do to manage this science and examine whether they should, in fact, consider halting it to allay their concerns and those growing among the public.

It was within this swirl that an international cohort of biologists together with a smattering of lawyers and physicians—about 140 in all—traveled to the Monterey Peninsula in California more than four decades ago. There, within a complex of Arts and Crafts–style buildings constructed just after the turn of the twentieth century, the scientists met. For nearly four days, they discussed the state of the science. When they emerged, they delivered what is now known as the Asilomar statement, a cautionary letter to scientists involved in recombinant DNA research. The letter, published in 1974 in *Science*, was disseminated throughout the scientific community and discussed in the popular press of the time.

According to many who have analyzed these events, the researchers' willingness to self-police and be accountable to the scientific community was rooted in their concerns for the safety of the science. Their actions also echo a "contract" science has had with society since at least the Second World War. At its most fundamental, argue Adam Briggle and Carl Mitcham in their 2012 text, *Science and Ethics*, that contract holds that society's progress derives from the "distinctive form of knowledge production" that comes from scientific inquiry, that is, ideas developed freely, and explored and vetted before being shared broadly. In exchange for this free agency, the public expects scientists to be accountable for the quality and safety of their research. That expectation of responsibility does not extend to the applications of research. Traditionally, note Briggle and Mitcham, that has been society's responsibility.


David Jones

That division is being increasingly questioned as science becomes more adept at teasing out the mechanisms that drive all of human biology. Calls to accept a greater degree of social responsibility for the use of their research have scientists considering anew how they can, or should, contribute to the public good.

Dear Mr. President

The structure of today's scientific research establishment, and its handshake agreement with society, can be traced to Vannevar Bush, an engineer who headed the U.S. Office of Scientific Research and Development through World War II. In late 1944, President Franklin D. Roosevelt wrote to Bush and asked him to analyze how the wartime scientific enterprise might be retooled to allow its application "in the days of peace ahead for the improvement of the national health, the creation of new enterprises bringing new jobs, and the betterment of the national standard of living."

In a report titled *Science: The Endless Frontier*, issued three months after Roosevelt's death, Bush called for strong centers of basic research set within the nation's academic institutions. It emphasized the need for a long-term commitment by the government to support the training of new generations of scientists and the pursuit of novel and existing avenues of research. It also proposed the establishment of an entity that would retain "discretion in the allocation of funds," ensuring "complete independence and freedom for the nature, scope, and methodology of research." Above all, it advocated for scientific progress, specifically the type that the report said resulted from "the free play of free intellects."

Public Eye

"Are scientists simply free actors, able to research whatever they want, or do they have an obligation to be socially responsible, to contribute to the public good?" asks David Jones '97, the A. Bernard Ackerman Professor of the Culture of Medicine at Harvard and the HMS Department of Global Health and Social Medicine.

"You can make a claim that they have an obligation because of their training. No matter how a scientist is funded at present—public funds, private donors, philanthropies, or corporations—everyone who is a practicing scientist now has had a substantial education in universities, and that training almost certainly involved a substantial investment of government research funds," says Jones.

"Scientists," he adds, "have some obligation to the public because of the investment society has made in them."

For scientists such as George Q. Daley '91, an HMS professor of biological chemistry and molecular pharmacology, the School's Robert A. Stranahan Professor of Pediatrics, and its dean designate, that obligation gets addressed on local, national, and international levels.

"I've struggled with these issues myself," says Daley, "and have engaged in deliberative processes with colleagues to consider our science and its implications. In doing so, I hope I'm providing a leadership example for the next generation.

"Scientists should be allowed to pursue their curiosity and creativity to discover new truths about the way the physical and natural worlds work, but how that work is applied, and whether certain work should be supported and others not, those discussions really have to involve the public."

A Firm Footing

Daley also directs the Stem Cell Transplantation Program at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center. In 2006, in his role as chair of an international task force on behalf of the International Society for Stem Cell Research, he helped develop a set of principles for self-governance and ethical conduct among his stem-cell research peers. Two years later, the group issued guidelines for the clinical translation of stem cell research, which included a firm statement against unethical efforts: "The ISSCR is deeply concerned about the potential physical, psychological, and financial harm to patients who pursue unproven stem cell-based 'therapies' and the general lack of scientific transparency and professional accountability of those engaged in these activities."

More recently, Daley and colleagues, under the auspices of the International Genomics Initiative, weighed in on embryo engineering using CRISPR technology and called for responsible behavior by scientists working in this galloping field. In April 2015, in *Science*, the group offered its collective thoughts on "a prudent path forward." Noting the potential slippery slope from disease curing to less acceptable applications, the group wrote, "it would be wise to begin discussion that bridges the research community, relevant industries, medical centers, regulatory bodies, and the public to explore responsible uses of this technology."

Daley says that although the waters can be choppy for scientists who enter into the debate on issues such as genome editing, it's worth the effort.

"These are difficult issues to navigate," says Daley, "but I think it's part of the responsibility of the scientist. It takes one outside of the comfort zone of just doing experiments and into the realm of interpretation.

"As scientists we invite peer review, we invite scrutiny of our animal research and independent scrutiny of work that involves human subjects. All this helps preserve the integrity of the research process.

"But issues like genome editing raise larger questions: What are the priorities of the research, and what are its applications from a social perspective? Is it something society should endorse? Such questions should be decided in a greater social context."

Surveys Say

Questions like those are fundamental to shaping how the public views the potential consequences of scientific research and how the scientific community approaches questions of social responsibility.

A 2016 Pew Research Center survey of 4,726 adults in the United States shows a nation wary of using biomedical technologies, especially to enhance human abilities. Asked how comfortable they were with technologies that allowed for gene editing to give infants a lifetime of reduced risk of serious disease, the implantation of brain chips to give people a greater ability to concentrate and process information, and the transfusion of synthetic blood to allow for greater speed, stamina, and strength, more than 60 percent of the respondents indicated they were very or somewhat worried about any such applications. The use of gene editing to prevent disease in children revealed the slimmest split, with 48 percent saying they would want such an option for their child and 50 percent indicating they wouldn't.

Respondents also thought the technologies might be outpacing scientists' understanding of the consequences of using them in humans. Seventy-four percent predicted brain chip implants would become available before the technology had been fully tested or understood, and 73 percent thought the same about the use of synthetic blood and gene-editing technologies.

George Q. Daley

Only a year before, in early 2015, the Ethics and Human Rights working group of the Science and Human Rights Coalition of the American Association for the Advancement of Science released findings from a pilot project that surveyed the scientific community on its responsibilities to society. The majority of the roughly 2,100 responses were from academic scientists in North America.

The working group's analysis showed that nearly 94 percent of respondents thought it was important to explain their work to the public, and 82 percent considered it important to engage in public-service activities. When considering the social responsibilities specific to their research, 92 percent said they thought they had an obligation to "serve in advisory roles in the public arena in their areas of expertise," and 88 percent saw a need to contribute to public policy deliberations in their areas of study. Interestingly, although nearly 96 percent thought it was important to "take steps to minimize anticipated risks associated with their work," only 82 percent felt it was vital to take steps to prevent the inappropriate use of their research by others.

Consider the Possibilities

A bone-deep concern over the inappropriate use of research could be said to have fueled Jonathan Beckwith's career as a scientist-activist.

In his nearly five decades at HMS, Beckwith, the American Cancer Society Professor of Microbiology and Immunobiology Emeritus, has often been a part of public debates on the safety, need, or ethical nature of research.

Early in his career, Beckwith led the research team that was the first to isolate a single gene, the *lac* gene. Despite the excitement generated by the work, one member of the team, Lawrence Eron '71, then a third-year HMS student, told a reporter for *The Harvard Crimson* that the research team was concerned that the technology it had pioneered in bacteria could be the first step toward genetically engineering humans. The team then called a news conference.

"We did talk about the science," recalls Beckwith. "but we also talked about what we thought were the social implications of the research. We thought the public should be more involved."

In the late 1960s, Beckwith introduced the social implications of science and historical perspectives on past research, blemishes and all, into a bacterial genetics course he was


Jonathan Beckwith

teaching. Two decades later, at the request of two former students from that class, Beckwith launched the Social Issues in Biology class at Harvard. That class still draws young scientists and medical students.

In the 1990s, Beckwith became involved in a small but significant movement to consider the ethical and social components of research. The Human Genome Project was taking off, and James Watson, of DNA fame, announced that 1 to 3 percent of the project's funds were to be used to study the ethical, legal, and social implications (ELSI) of the research.

Beckwith was named to what became known as the ELSI committee for that project. He credits the effort with not only informing the public about the genome project but also in seeding a field of inquiry that continues to affect social policy. In a 2007 interview in *BioEssays*, Beckwith noted that the ELSI phenomenon was embraced elsewhere in the world, leading to a body of research on issues related to genetic testing programs.

The importance of educating the next generation of scientists continues to figure large on Beckwith's radar. He co-wrote a 2005 commentary in *Nature Biotechnology* that included a proposal that graduate-level science education include the study of the social implications of science and the historical instances where scientists have raised concerns about the use of research. Although that proposal has yet to be acted upon, Beckwith was pleased to note a recent change to the Training in the Responsible Conduct of Research guidelines issued by the National Institutes of Health for grants that fund instruction and training.

That change, which took place in 2009, urges grant applicants to develop pedagogies that include instruction on "the scientist as a responsible member of society, contemporary ethical issues in biomedical research, and the environmental and societal impacts of scientific research."

"Not many people may have noticed that change," says Beckwith, "but I think it's a particularly important one."

Carry On

Just as having scientists who are comfortable discussing the effects of science in the marketplace has become vital to the scientific community, the preparation of young physicians for the responsibilities of translating science for their patients has taken an ever-larger role in medical education. It's an education that should continue, according to their profession's ethical code.

Within the American Medical Association's nine Principles of Medical Ethics, which anchor the larger AMA Code of Medical Ethics, sits this precept: "A physician shall continue to study, apply, and advance scientific knowledge, maintain a commitment to medical education, make relevant information available to patients, colleagues, and the public. . . ."

From his vantage as a physician-scientist, Daley underscores the principle's importance.

"Physicians are often the interface between patients and new technologies," he says. "I think it's incumbent upon clinicians to understand new technologies and to continue to educate themselves, whether it's on stem cells or novel applications of gene editing. The clinic is where these issues get played out."

Jones considers these patient-doctor responsibilities continually. Together with Edward Hundert '84, the School's dean for medical education, Jones oversees the Pathways curriculum's social and population sciences courses. The course explores everything from truth-telling, reproductive ethics, patients' capacity to make informed decisions, and the ethical dilemmas faced by medical students to the responsibility that physicians have to relieve health inequities and help their patients achieve the best health outcomes. The goal is to address "the role of the physician and the moral framework of modern health care practice."

"One role physicians have," says Jones, "is to serve as the mediator, or the translator, between patients and the basic science community. I think this gives physicians a real obligation to be intelligent evaluators of science so that they can educate patients and help them make the most appropriate medical decisions."

The payoff for preparing young minds for the ethical dilemmas that arise within their profession was recently made clear to Beckwith. He had been invited to attend a seminar in the Department of Genetics. The speaker was Ethan Bier, a professor of cell and developmental biology at the University of California, San Diego. Curious, Beckwith accepted.

Beckwith learned that the speaker had been a graduate student at HMS years ago, so after the presentation, Beckwith approached Bier.

"I felt stupid doing this," Beckwith recalls, "but I asked him, 'Do I know you?'"

"I was a student in your class," Bier responded. He had taken Beckwith's bacterial genetics course.

They sat down to talk. "Bier told me, 'I wanted to see you to thank you for what you taught me.'" Explains Beckwith, "He was talking about the social implications material we covered in the course."

Beckwith paused. "Bier then told me the course had made him think about those issues and that it helps him think about those things in his research today."

What is Bier's work? Gene drives, which are naturally occurring molecular elements that actively influence the heritability of the genetic material of any sexually reproducing species.

Recently, gene drives have been built using CRISPR technology with the aim of one day controlling the spread of viruses such as Zika. It's work that at least one newspaper described as technology that offers life-transforming power. ■

Ann Marie Menting is the editor of Harvard Medicine *magazine.*

As preparations ramped up for possible U.S. involvement in World War II, isolating a blood substitute for transfusion became a military priority.

To address this need, in 1940, Walter Cannon, HMS Class of 1900, then head of the National Research Council's Committee on Transfusions, called on Edwin Cohn, head of the Department of Physical Chemistry at HMS. Cohn and his lab were ready, having laid the groundwork through their work on the physicochemical properties of protein components, including serum albumin and serum globulin.

Cohn's work for the Army coincided with the American Red Cross's campaign to establish a national blood donation program for the war effort. His lab and the Red Cross developed a symbiotic relationship: in 1941 a group of Red Cross volunteers began making weekly blood donations that were delivered to Cohn's lab.

These donations provided the raw material to develop what became known as the Cohn process for fractionation—extracting albumin and other clinically usable products from plasma while maintaining the structural and functional integrity of the protein.

Half a world away and a couple of years later, Edward Churchill, HMS Class of 1920, in his role as Consultant in Surgery, Fifth U.S. Army, in North Africa, observed the effects of overreliance on plasma in cases of shock, and, in a report to the surgeon general in the region, wrote, "there is a need for whole blood transfusions in the treatment of a significant proportion of wounded. Plasma is not an adequate substitute in these cases."

Churchill set up "live-blood" banks in Tunisia, which recruited donors from troops not actively engaged in combat or recovering from injuries. Reporting this story in August 1943, the *New York Times* noted that "blood is taken only from volunteers at present."

In his memoir, *Surgeon to Soldiers*, Churchill wrote that "the Red Cross's and the National Research Council's commitment to plasma and plasma fractionation reflected a huge vested interest [which] had been built up starting from assumptions and erroneous thinking."

—*Susan Karcz*

The small centrifuge devised by Edwin Cohn to separate whole blood into blood cells and plasma evolved over the years from an apparatus made of glass to one manufactured from stainless steel. Later refinements by others include this single-use plastic centrifuge, called the Latham Bowl.

WARREN ANATOMICAL MUSEUM AT THE FRANCIS A. COUNTWAY LIBRARY (CENTRIFUGE); JOHN SOARES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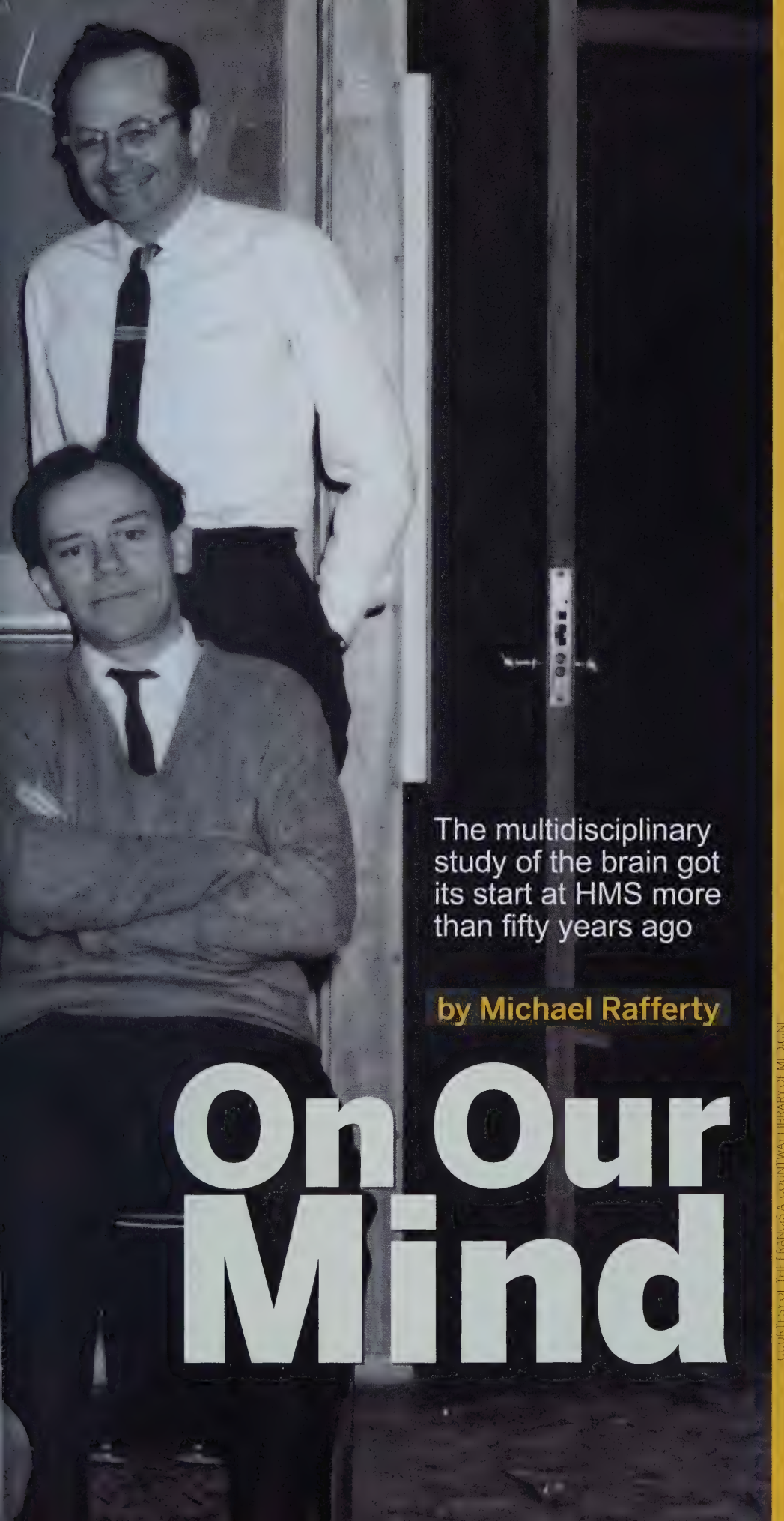


The multidisciplinary study of the brain got its start at HMS more than fifty years ago

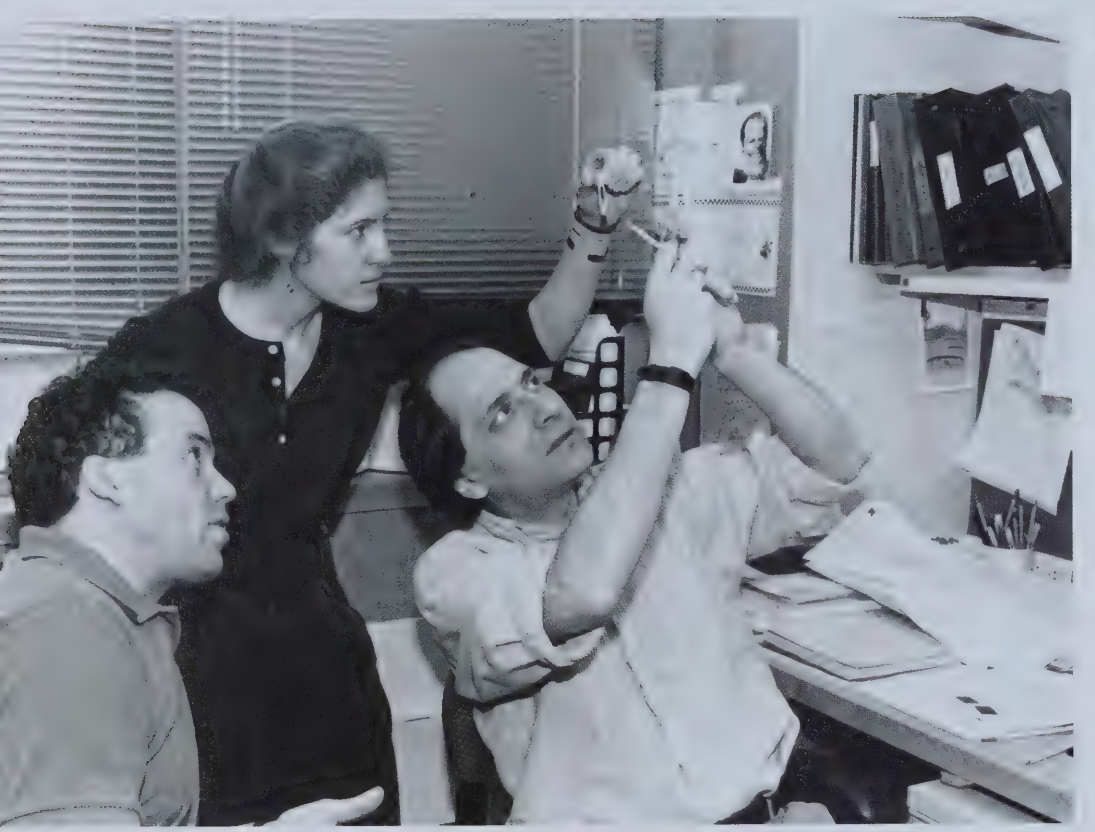
by Michael Rafferty

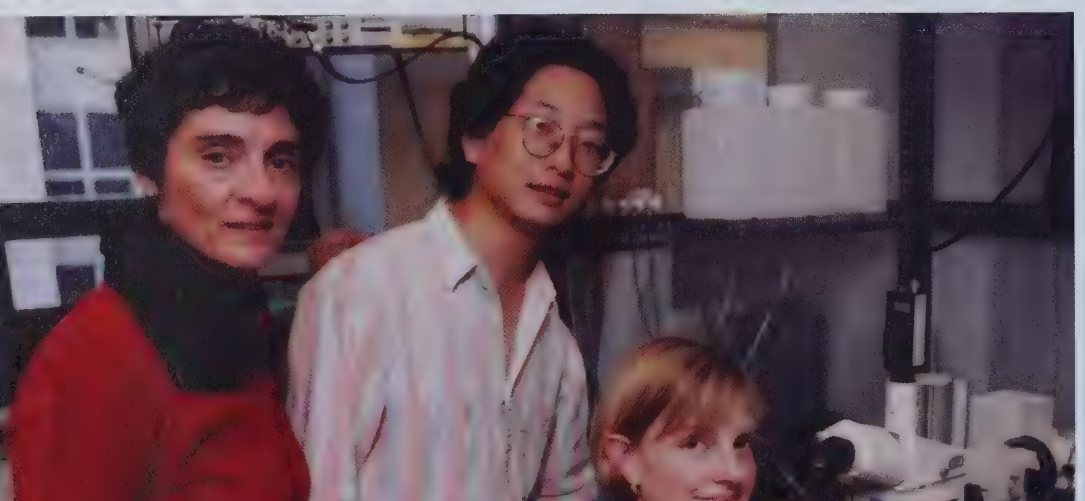
On Our Mind

ALL TIED UP: The HMS Department of Neurobiology began with a group of six researchers, led by Stephen Kuffler (center, standing). Helping him establish what became the nation's first academic department to study the brain from a multidisciplinary perspective was David Hubel (clockwise from near left, standing), Torsten Wiesel, Edward Kravitz, David Potter, and Edwin Furshpan.

COURTESY OF THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE

Today, most science watchers know that the stereotype of the solitary scientist chipping at one sliver of a question after another is myth. Time and again, we learn of breakthroughs that result from the coordinated work of a research team—individuals from various disciplines contributing their expertise to the resolution of shared questions. ■ When discoveries are achieved, scientists celebrate, perhaps with a toast to the publication of a particularly insightful paper or simply with a get-together to acknowledge the work of the team. ■ When, however, a discipline has the opportunity to mark not only decades of discoveries but also a revolutionary approach to how research in that discipline is undertaken, its practitioners turn to ceremony to reflect, reminisce, and recommit to their life's work. ■ So it is in 2016 at HMS, where the Department of Neurobiology, the nation's first academic entity conceived of and built upon the multidisciplinary study of the brain, is marking a half-century of collaboration and discovery.





GENERATIONS OF TEACHERS: Current chair of neurobiology Michael Greenberg (top photo, white shirt) led a laboratory that included Margaret (Tam) Thompson and David Ginty. During her tenure as department chair, Carla Shatz (below, in red) worked with Gene Huh and Lisa Boulanger.

Hemispheric Changes

Any story that goes back fifty years inevitably starts even further back, and often includes an element of serendipity. For HMS neurobiology, that element can be traced to Australia and tennis.

In the late 1930s, the two came together in a life-changing way for Stephen Kuffler, a native of Hungary who had earned his medical degree at the University of Vienna. Kuffler's memoir was included in an article written by Bernard Katz, a biophysicist who shared the 1970 Nobel Prize in Physiology or Medicine for his work on nerve biochemistry, and published in 1982 in the *Biographical Memoirs of Fellows of the Royal Society*. According to that memoir, Kuffler emigrated to England after the Nazi invasion of Austria, then opted to relocate to Australia, perhaps in the hope of being able to practice medicine again. Shortly after beginning a job at the University of Sydney, he was introduced to a researcher at the university, one who happened to be looking for a tennis partner. That researcher was John Eccles, a neurophysicist who would share the 1963 Nobel Prize in Physiology or Medicine for his work on synapses.

Game, Set, Match

Theirs proved to be a good tennis pairing. That successful collaboration led to another when Kuffler joined Eccles's lab. In 1939, Katz, too, joined the lab. Being mentored by Eccles and Katz, two established leaders in the study of neuronal physiology, proved significant for Kuffler for it helped him realize that brain research required the perspectives of different disciplines. That realization set the stage for his new vision for research in a field he called neurobiology.

In 1941, Kuffler achieved international notice for achieving the first isolation of a single muscle fiber together with its neuronal connection. He was invited to join the physi-

The lab's stature was further enhanced when Hubel and Wiesel published their work on the visual cortex. This work offered one of the earliest indications that the brain is shaped by experience as well as genetics—a concept fundamental to brain plasticity.

ology faculty at the University of Chicago in 1944, and, in 1947, began a twelve-year stint at what was then the Johns Hopkins University Medical School. There, according to the article by Katz, Kuffler worked on the mammalian retina and stretch receptor neurons in crustaceans. He also built a cohort of colleagues who, in 1959, moved with him to HMS. That cohort included researchers who would become the core of the School's nascent neurobiology department, a group Kuffler referred to as "the boys": Edwin Furshpan, David Hubel, David Potter, and Torsten Wiesel.

A Vision Realized

With the addition of Edward Kravitz in 1960, the team's membership totaled six, all working in a neurophysiology laboratory housed within the HMS Department of Pharmacology. But Kuffler was already building support among the HMS faculty for a new department. When Otto Krayer, the chair of pharmacology, announced his retirement in 1965, Kuffler was ready to act.

According to Kravitz, now the George Packer Berry Professor of Neurobiology at HMS, "Dean Robert Ebert came to Steve and said, 'Would you like to be the chair of physiology or pharmacology?' Steve said he didn't want either, that he wanted to start an entirely new department, one that brought expertise from several disciplines to the study of the brain."

In 1966, the HMS Department of Neurobiology was launched; a chart of the new department may well have looked like a crowded Venn diagram, its overlapping circles representing physiology, biochemistry, neuroanatomy, and electrophysiology.

Good Chemistry

Even before the department's name was painted on the door, its members had made some significant contributions to the field. Says Kravitz, "We had produced some important results, including staking out our position on a heated international debate over the fundamental nature of neural transmitters."

That position evolved from work published in *Nature* in 1962 by Potter, Kravitz, and others, in which they showed in lobsters that an amino acid called gamma-aminobutyric acid (GABA) was produced by the neurons and could inhibit or slow neuronal activity. Until that time, neurotransmitters, substances that regulate the movement of signals from one brain cell to another, were thought to be electrical entities only. GABA, by comparison, was a chemical. The *Nature* paper provided the first definitive proof that GABA was an inhibitory chemical made by neurons and laid the foundation for work on GABA in the mammalian brain.

The lab's stature was further enhanced one year later when Hubel and Wiesel published their work on the visual cortex. In describing columns of cells that receive, refine, and pass along images from the retina, they demonstrated how those images come into focus in the brain and introduced the concept that experience can shape the brain's circuitry during what they described as "critical periods" in early life. This work offered one of the earliest indications that the brain is shaped by experience as well as genetics—a concept fundamental to brain plasticity. This research by Hubel and Wiesel earned them the 1981 Nobel Prize in Physiology or Medicine and further bolstered the department's reputation for innovation and discovery. Before his death in 2013, Hubel was the John Enders University Professor and an emeritus professor of neurobiology at HMS; Wiesel is the Vincent and Brooke Astor Professor Emeritus at The Rockefeller University.

Transitions

Kuffler had cultivated a forward-thinking culture among the department's researchers and that philosophy remained in place when he died in 1973. Wiesel became the new chair, followed in 1982 by Potter, now the Robert Winthrop Professor of Neurobiology Emeritus. During their respective terms leading the department, each continued to recruit faculty who brought diverse expertise to the group. Many of those selected were visionary and enterprising in their own ways. Several would later start up programs in neurobiology at other universities.

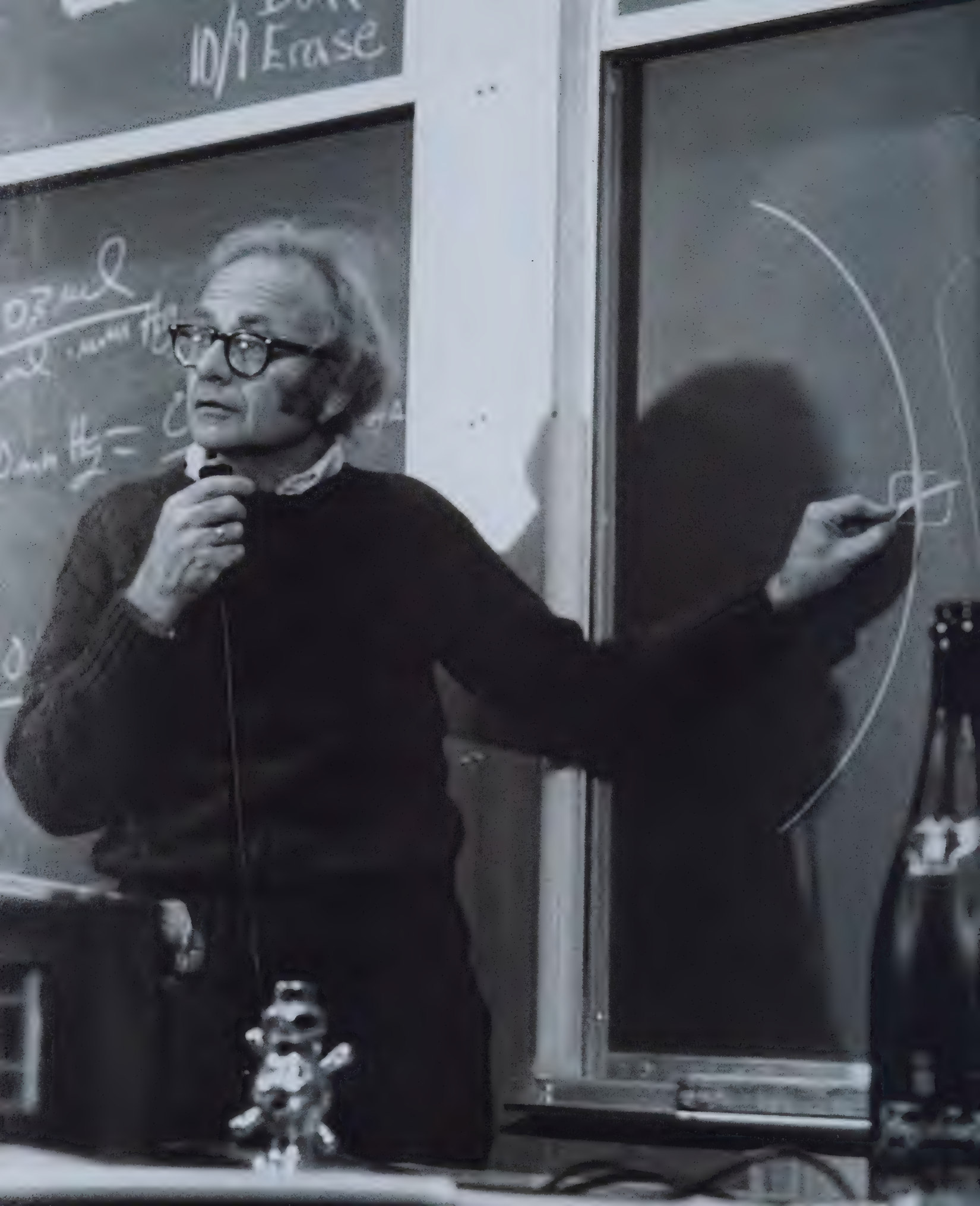
Two examples of this legacy are neurobiologists Zach Hall, who created an interdepartmental neurobiology program at the University of California, San Francisco, and Story Landis, who was the director of the Center on Neurosciences at Case Western Reserve University School of Medicine. Hall and Landis later each served as director of the National Institute of Neurological Disorders and Stroke.

Making Sense of the Senses

The early work by Eccles and Katz, as well as the work now underway in the department, has contributed to our understanding of the pathways of sensory information to the brain and have led to a greater understanding of the mechanisms of neural activity.

With each decade, department faculty expand our understanding of how sensory information—the stimuli our eyes, ears, skin, and other sensory organs receive from the world we live in—is interpreted by our brains and shapes our behavior. Examples of some of the areas in which researchers in the department made contributions include the discovery of the mechanism by which the nervous system changes to respond to chronic pain; description of the functionally distinct regions for the processing of form, color, motion, and depth in the visual systems of primates; development of molecular and biophysical analyses of auditory hair cells; and explanations for how odor receptors are organized in the nose, how they organize into the olfactory bulb, and how the information gathered by the olfactory neurons is processed in the brain's cortex. The olfaction work, some of which was undertaken by Linda Buck during her tenure at HMS, later earned her and another researcher in the field the Nobel Prize in Physiology or Medicine.

Buck had been recruited to the department by Gerald Fischbach, who became chair in 1990. Although Fischbach, currently vice president for health and biomedical sciences at Columbia University and chief scientist and fellow at the Simons Foundation, had not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TELESCOPING TIME: David Hubel (opposite) delivering a lecture on the work that led to the Nobel Prize in Physiology or Medicine, which he shared with Torsten Wiesel (below with Hubel at a news conference following the award announcement). The department's 50th anniversary celebration brought together the remaining founders: Wiesel (clockwise from far left, standing), Furshpan, Kravitz, and Potter.

been a part of Kuffler's original group, he took its traditions to heart by hiring and retaining faculty who brought their own diverse fields of expertise. So, too, did Carla Shatz when she took the helm of the department in 2000.

Shatz, now a professor of neurobiology and biology at Stanford University and director of Bio-X, Stanford's interdisciplinary institute, represented two firsts for the department: She was the first graduate of the HMS department (PhD 1976) to become its chair and the first woman to lead it. Her connections to the department went even deeper. While a student at Harvard College, Shatz worked on her honors thesis in chemistry in the lab of Hubel and Wiesel. Later, Shatz carried out her PhD work with Hubel and Wiesel.

The Long View

When Michael Greenberg, the Nathan March Pusey Professor of Neurobiology at HMS, was appointed chair of neurobiology in 2008, he, too, felt at home in the interdisciplinary tradition that had been fostered since Kuffler's founding of the department. Greenberg, however, has his own vision of how that tradition would be expressed in the twenty-first century.

"We need to bring people together, as Kuffler did, but on a grander scale," says Greenberg. "We need expertise in physics, chemistry, and biology as well as in divisions within each discipline, and we need mathematics, engineering, molecular biology, and genetics. We need a lot of fields to come together."

After years of discovery related to the brain's mechanisms—neurons, synapses, and transmitters—the research of recent decades has begun to investigate connections: how groups of neurons communicate, how extensive and interconnected the network of brain cells is, and what interplay exists among the molecular mechanisms that shape or control neuronal function and sensory input.

Neurobiology faculty, for example, are applying engineering fundamentals to investigations of how decisions are made, and they are using computational tools to theorize how networks of neurons translate sensory information and use it to make behavioral decisions. Others are combining genetic tools and electrophysiological techniques to tease out how sensory stimuli, particularly sound and smell, are processed; devising better tools for imaging neurons, including the minute extensions called dendrites that communicate signals; and using circuit mapping, molecular genetics, and behavioral analysis to elucidate the intricacies of touch.

When Greenberg thinks about the early days of the department, he acknowledges, "it was a fantastic time to be a neuroscientist because many fundamental, exciting, transformative discoveries were being made.

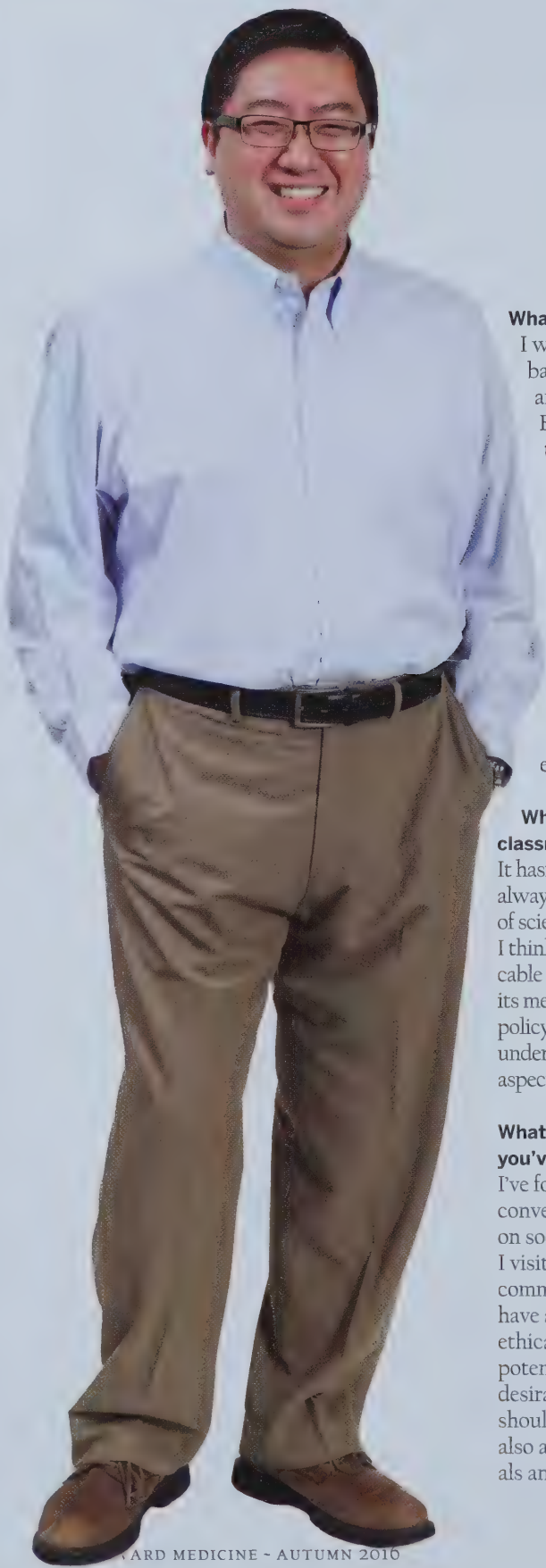
"But this is a field where there's still much more to be discovered that's equally exciting. The collaborations among researchers in this department will not only continue to provide important insights into brain development and function but will also provide the key to understanding neurological and psychiatric disease.

"It's a great time to be a neuroscientist." ■

Michael Rafferty is a Massachusetts-based science writer.

FIVE QUESTIONS

FOR JOHNNY KUNG ON GENETICS LITERACY



Research Associate, Department of Genetics, Harvard Medical School

Director of New Initiatives, Personal Genetics Education Project

What first caught your scientific fancy?
I was always fascinated with exploring my backyard, looking at plants and animals, and understanding how nature works. Eventually I knew I wanted to make this interest a career. One of my science heroes is Charles Darwin; I admire his dedication to understanding nature and his care in teasing out how nature works. In my own research, I studied X-chromosome inactivation, the process that shuts down one of the two X chromosomes in each cell of the female mammal during embryonic development. I loved doing a deep dive into the molecular mechanisms by which certain RNAs turn genes, or entire chromosomes, on or off.

What made you shift from the lab to the classroom?
It hasn't been that much of a shift, really. I've always been interested in the social dimensions of science as well as in physiological processes. I think that for scientific research to be applicable to society and to most equitably benefit its members, everyone, including researchers, policymakers, and the general public, needs to understand the broad social, ethical, and legal aspects of genetics research.

What have you learned from the people you've visited in community settings?
I've found there is genuine interest in having conversations about the impact of science on society. When my pgEd colleagues and I visit classrooms, congregations, or other community groups, the people we talk with have a lot of good questions about emerging ethical issues of genetics research, such as its potential use to select or modify offspring for desirable traits. What we call genetic literacy should not be about the science only, but also about how genetics relates to individuals and families.

What are the benefits to taking genetics education "on the road"?
New genetic technologies are coming, and they will affect society. People can, and perhaps should, help shape how these tools are developed and used. If all members of society become aware of what the tools of genetics can do and cannot do for them, they will be in a better position to decide whether or how to integrate those tools into their lives. Genetic testing, for example, can have many beneficial uses, but there are concerns about privacy, about discrimination. By becoming aware, people can make informed decisions about whether to undergo genetic testing.

What one thing would you like people to know about personal genetics?
I think it's important to know that genetics is not deterministic. Your genetic makeup does influence how you develop and what your risk is for certain diseases, but there's more at work than just what's in your DNA. Environmental influences, such as where you live, the behaviors of people you live with, even who and what you encounter when you walk out your front door, all affect how what's in your DNA will manifest. It's never as simple as isolating one gene as the cause for something. —*Susan Karcz*

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ALUMNI COUNCIL REPORT

Council members attending the May 2016 meeting heard updates on several HMS programs, including reports from Ed Hundert '84, dean for medical education, and Stephanie Hunt, director of financial aid, on how the implementation of the School's Pathways curriculum is progressing, on the state of student financial aid, and on efforts to meet the financial needs of students in a time of fiscal concern.

The curriculum rollout is getting excellent reviews from students, Hundert said. Hunt outlined the status of the aid available to students and the increasing challenge to match the competitive financial packages being offered to HMS candidates by peer schools. Calls were made to better market the aid program and to encourage alumni to continue to support it.

Nancy Oriol '79 and Dea Angiolillo '79, co-chairs of the Student Alumni Advisor Network, reported on efforts to improve connections between alumni and new graduates, and Carolyn Walsh '09 updated attendees on the Welcome to Your City program, which links alumni with residents new to their cities.

Alumni Fund Chair Tamara Fountain '88 told attendees that alumni donations were on track to exceed the year's $2.6 million goal .

The meeting was marked by good-byes, too. Departing Dean Jeffrey S. Flier recounted some of the highlights of his years as dean, and Michael LaCombe '68 received the Council's thanks for his year of service as its president. James J. O'Connell '82 is the incoming Council president.

John Maa and Helen Yu

Fodor's for Residents

Program aims to help fourth-year HMS graduates feel at home with their residencies—and their new cities

THE DEMANDS OF A RESIDENCY can be such that building a life outside the hospital seems impossible. When that residency is based in a city you're unfamiliar with, the sense of being disconnected can compound.

Welcome to Your City, a program developed by Carolyn Walsh '09, currently the first pentad's representative on the HMS Alumni Council, seeks to help HMS alumni who've started residencies in cities outside Boston to feel comfortable in their new communities. The program, now in its second year, does this by matching fourth-year HMS graduates with alumni in the cities where they will start their residencies.

One such connection took place in San Francisco in 2015, when John Maa '94 and Haining (Helen) Yu '15 introduced themselves to each other.

"I received an email from John," Yu recalls, "telling me that we'd been paired through the program. He asked if I'd like to meet sometime."

"It was nice to develop the connection," adds Yu, "and to talk to someone who had moved from the East Coast to the West Coast and had been through what I was starting to go through."

For Maa, the link had an unexpected result: It reminded him of the important role that mentors had played in his own career development.

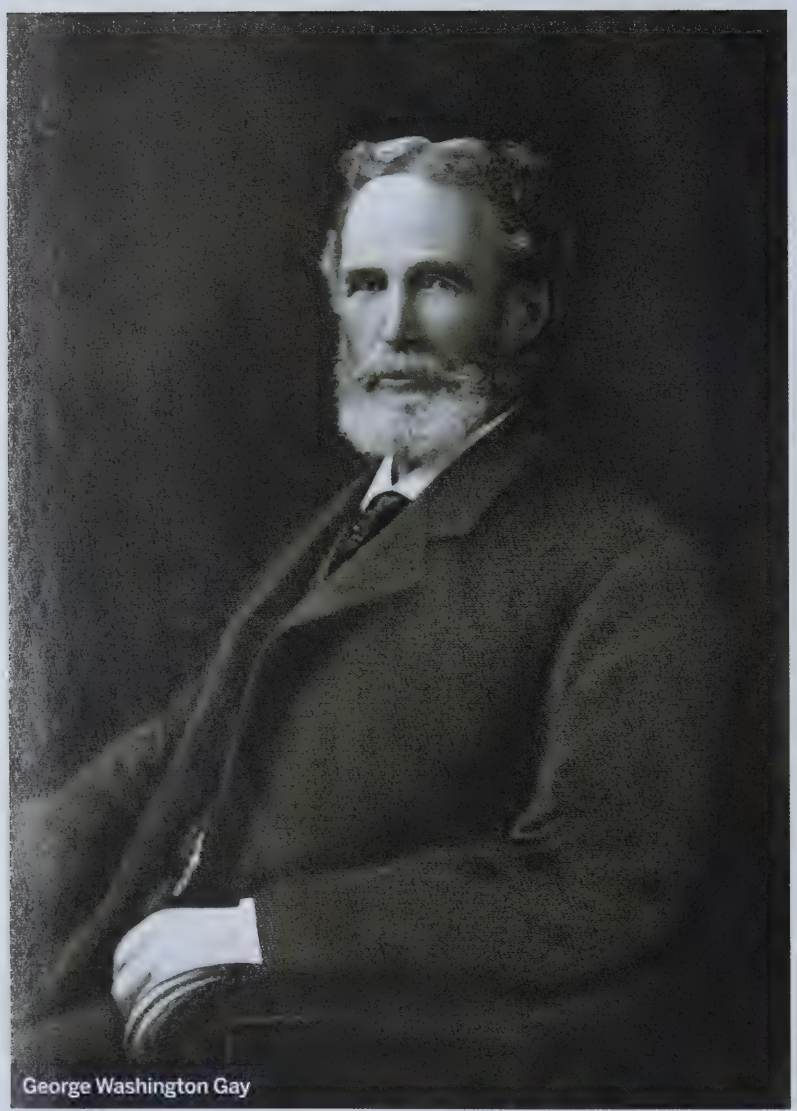
"I do a lot of surgery, public policy, and government work," says Maa. "It's valuable to have people who have gone ahead of you and know the opportunities, collaborators, pitfalls, and lessons learned. The importance of receiving support from others cannot be overemphasized."

Although Maa has focused on surgery and Yu is interested in pursuing psychiatry, they quickly found their professional common ground. Yu is finding Maa's experience in public policy and government to be useful as she develops her interests in public policy and advocacy for better services for people with mental health issues. For Maa, Yu has been a source of reconnection to his goals.

"Talking with Helen about her hopes and aspirations has allowed me to look back on the goals I had when I graduated," he says. "I realized that most of my strongest career mentors in San Francisco actually went to HMS. Because of those connections, I think the work I've done has gone beyond my early expectations.

"I hope that I can be that type of mentor to Helen."

—Ann Marie Menting



George Washington Gay

AN OUNCE OF PREVENTION

A lecture series on ethics in medicine began a century ago with a gift from an alumnus

IN 1917, the President and Fellows of Harvard College received a letter from George Washington Gay, Class of 1868. A successful surgeon, Gay had worked long enough in his profession to identify what he believed would be an important addition to the training of young physicians.

"Realizing the fact that young physicians not infrequently make embarrassing mistakes in medical ethics through ignorance or thoughtlessness," he wrote, "I beg leave to establish a permanent fund for lectures upon the wise and proper methods of conducting the business of physicians, as it relates to fees, collections, investments, etc." Included with the letter was a gift of $1,000, the equivalent of nearly $19,000 in inflation-adjusted 2016 dollars, which was used to establish the George W. Gay Lectureship, the oldest endowed lectureship at HMS—and possibly the oldest medical ethics lectureship in the United States.

Gay also was ahead of his time in his practice of medicine. After receiving his medical degree from HMS, the Boston-based surgeon earned widespread acclaim at a young age for handling a number of critical cases. This success gave him the freedom to establish one of the largest private practices in the region.

A visiting and then senior surgeon at Boston City Hospital from 1872 to 1899, Gay also served as a longtime instructor in clinical surgery at HMS beginning in 1888. His accomplishments earned him an honorable position among the highest-ranking U.S. surgeons of his time.

The Gay Lectureship has hosted many of the nation's most influential physicians, scientists, researchers, and social observers who have come to campus to share their experiences and perspectives with the Harvard community. Past speakers have included Marian Wright Edelman; Erich Fromm; Nicholas Kristof; Margaret Mead; Francis Weld Peabody, Class of 1907; Elizabeth Kübler Ross; and Elie Wiesel.

Though he died in 1931, Gay had prepared a trust bequeathing funds to HMS. In 2015, that trust directed more than $8.5 million to HMS, which would be allocated as unrestricted funding to be used at the discretion of the dean and to establish a scholarship to support students with demonstrated financial need. *—Laura DeCoste and Kate Harper*

Phineas Gage

Phineas Reimagined

A daguerreotype reveals the man behind the story

A DAGUERREOTYPE of Phineas Gage, a rail worker who lived in the mid-nineteenth century, recently entered the Gage collection in the Warren Anatomical Museum, joining other artifacts of what has become known as the American Crowbar Case. The roughly 3-inch square image shows Gage holding the tamping iron that blew through his skull in a workplace accident that occurred more than 160 years ago. In the daguerreotype, Gage's face is far less disfigured than might be expected, given his accident. His level gaze engages the viewer directly.

It is an image of Gage that surprises and delights researchers.

"You can read an amazing amount into a picture," says Dominic Hall, curator of the Warren Anatomical Museum at the Center for the History of Medicine in the Francis A. Countway Library of Medicine. "There was a time when he was exhibiting himself at shows, and this might have been a publicity photograph for that."

The daguerreotype provides new information on the Gage case. Some think it suggests that toward the end of his life Gage had made a social recovery and wasn't as compromised as most have assumed.

Gage's case has become a textbook example for studies on posttraumatic social recovery, white-matter connectivity, and frontal-lobe function. His place in the history of neurologic trauma began on September 13, 1848, in Cavendish, Vermont. Gage was using a 3-foot 7-inch long, 13.25-pound tamping iron to pack explosive powder into a railroad bed when the powder ignited and propelled the 1.25-inch diameter rod through the skull of the 25-year-old man. The bar severely damaged the optic nerve in Gage's left eye and removed a fragment of his brain.

Although he survived, many observers said the accident changed Gage. His physician, John Martyn Harlow, noted that Gage's behavior had become inconsistent and that his language and actions had taken a grotesque turn. Harlow's observations suggested a link between Gage's personality change and trauma to his brain's frontal lobe.

The daguerreotype was donated by vintage photo collectors Jack and Beverly Wilgus. The Wilguses had purchased the image thinking the man pictured was a whaler. But in 2008, after some exchanges on social media, they learned that the man in the photograph was Phineas Gage.

—Sara Silvestro

CLASS NOTES

NEWS FROM ALUMNI

1951

Gerald Foster

I retired from my clinical practice in 2006. At HMS, I continue to teach the introductory clinical course, administer the objective clinical examination, and interview candidates for the Committee on Admissions. I am also active on the Financial Aid Committee.

Grateful patients have endowed the HMS Gerald S. Foster Academy Associate Professor of Medicine, with Kate Treadway as the first incumbent. An endowed Gerald S. Foster Scholarship has been established with unique provisions. The Committee on Admissions selects one student in each entering class to be a Foster Scholar based on the candidate's academic record and a demonstrated commitment to public service. The student receives a $40,000 reduction of debt at graduation. There is also an award to a graduating student for service on the Committee on Admissions.

This is my 65th year at Massachusetts General Hospital and HMS, and I am grateful for all the opportunities that I've had.

1952 65th REUNION

Samuel Katz

After twenty-two years as the chair of pediatrics at Duke University, I am now an emeritus faculty member working part-time as a consultant to several international vaccine programs in the Duke Human Vaccine Institute. My wife, Catherine Minock Wilfert '62, has retired after ten years as international director of the Elizabeth Glaser Pediatric AIDS Foundation. We reside happily in North Carolina with eight children and seventeen grandchildren between Washington, DC, and California.

1956

W. Banks Anderson, Jr.

My wife, Nancy, and I recently attended an event in San Francisco celebrating the centennial of certifications awarded by the first medical specialty board in the United States. The American Board of Ophthalmology invited all current and former members of its board to a festival in the Palace Hotel, where so many of our West Coast oral exams are given. It was a pleasure to catch up with colleagues and spouses whom we had not seen for years and to review what had transpired since the certifying of those first seven diplomates in 1916.

Richard Sogg

I've been busy at the piano this year, having performed a new work for flute, piano, and strings by a contemporary composer, Nancy Bloomer Deussen. I also gave my annual home concert in June, playing a work by the young Beethoven—the trio for flute, bassoon, and piano—and a work by the more experienced Beethoven—the sonata for French horn and piano and numerous pieces for voice and piano. And for something completely different, in April I acted in a reading of the stage version of *The Diary of Anne Frank*.

1957 60th REUNION

Mark Kartchner

Midway through my surgical residency at Massachusetts General Hospital, I volunteered as the chief surgeon for a two-year tour of duty with the Indian Health Service in Lawton, Oklahoma. I then spent a year training in the new field of vascular surgery with **Jesse Thompson '43** in Dallas and later established a vascular practice in Tucson, Arizona.

Since I retired from active clinical practice in 1999, I have continued to assist in surgery under the auspices of Esperança, a charitable organization providing medical care in poor countries. I was very involved in developing a self-funded volunteer surgical program in Bolivia, and more recently, with the assistance of my twin, Max, an anesthesiologist, established a similar volunteer surgical program in Nicaragua.

I will always be grateful that I was privileged to represent the HMS tradition of extending and providing care for the less fortunate of the world. I believe that any measure of success I have achieved is attributable to that tradition.

1962 55th REUNION

Steven Jonas

I am supposedly retired, but have totally failed the subject. I recently published my thirty-sixth book, *Ending the "Drug War"; Solving the Drug Problem: The Public Health Approach*. The book proposes an entirely new approach to dealing with the use of what I call recreational mood-altering drugs. The two most widely used are, of course, tobacco products and alcoholic beverages. The program I propose would enable us to both deal with the drug problem and end the useless, costly, and highly destructive drug war.

1968

Stephen Hochschuler

I am one of the cofounders of the Texas Back Institute in Plano, Texas, and a founding member and past president of the International Society for the Advancement of Spine Surgery.

As an orthopedic spine surgeon, I have dedicated my life to actively advancing spine-saving technologies and techniques. My partners at the institute and I have published peer-reviewed research, participated in FDA trials, and have trained more than one hundred spine fellows nationwide.

I am married with four adult children. I enjoy traveling and bicycling and am a fitness enthusiast. In my most recent travels, I've visited Cuba, Switzerland, and Costa Rica.

1973

Howard Freedman

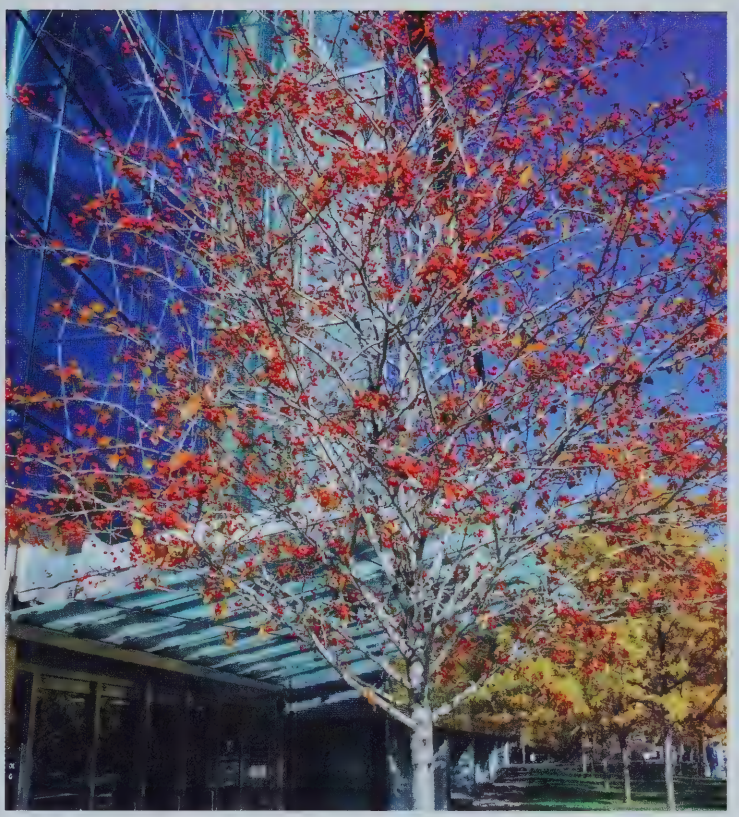
Pam and I are busy relaxing on our 44-foot catamaran, *Helios*, anchored in the British Virgin Islands. We spend half the year on the boat sailing around the islands, mostly sitting in anchorages. I enjoy scuba diving, windsurfing, and Hobie catamaran racing at the Bitter End Yacht Club.

When at home in Naples, Florida, we are very busy. I am deeply involved in volunteer work: running a free eye clinic, doing vision and hearing screenings on preschool children with the Lions, and helping to run our Naples Lions Club and the Harvard Club of Naples.

I look forward to seeing any classmates who venture down to Naples, winter or summer.

Steven Weinberger

I retired from my position as executive vice president and CEO of the American College of Physicians in September. This past summer, Janet and I started our transition to retirement in Italy with Patty and **Mike Rosenblatt**, Cheryl and **Jim Reinertsen**, and Doris and **Doug Yock**.



1974

Thomas Najarian

It was great to see classmates who came to the most recent reunion. I've retired from seeing patients but continue to do research with three ongoing studies at Stanford. Two placebo-controlled studies are now looking at Qsymia, my weight-loss treatment now on the market for use in bulimia and binge eating.

My wife, Sue Unkel, and I would like to extend an invitation to classmates to get in touch and set up a time for a free vacation visiting us in Lake Tahoe. We'd love the company.

1979

Larry Dewey

I have worked for the VA since 1983, treating vets with all types of psychiatric problems and managing various clinical programs. I have loved seeing vets, and I have loved practicing psychiatry. I got a great deal of satisfaction out of helping to start a psychiatry residency in Idaho, a state with the lowest number of psychiatrists per capita in the nation, in partnership with the University of Washington, local medical centers in Boise, the state of Idaho, and the VA. I am currently enjoying semiretirement working half-time at a small VA outpatient clinic in Orem, Utah.

Because I could never find anything substantive that discussed how killing people in various ways affected those who did the killing over the course of their lives, I finally wrote and published *War and Redemption: Treatment and Recovery in Combat-related Posttraumatic Stress Disorder* in 2004. I hope to do a second edition, incorporating all I have learned from current wars and the soldiers who have fought in them, in the not-too-distant future. I am very grateful to have a great wife, Teresa, who taught me how to write decently!

1981

Ilonna Rimm

After four years of preparation, I received a chartered financial analyst designation, likely becoming the only MD/PhD/CFA on the planet. I continue to have great enthusiasm for health care investing as an opportunity to participate in the health care innovations that have lengthened all of our lives. In my free time, I made my stand-up comedy debut, which is listed under my name on YouTube. Check it out!

1985

Elizabeth (Lisa) Petri Henske

I live in Cambridge with my husband, Rob. I'm the director of the Center for LAM Research and Clinical Care at Brigham and Women's Hospital. I'm also director-elect of the Brigham Research Institute and an HMS professor of medicine. LAM (lymphangioleiomyomatosis) is a rare destructive lung disease in women caused by mutations in the tuberous sclerosis complex genes.

1986

William Rosenberg

I founded the Cancer Pain Research Consortium, an international multidisciplinary nonprofit organization of physicians and other care providers dedicated to improving through research, education, and awareness, the care of patients suffering cancer-related pain. Our members include medical and radiation oncologists, neurosurgeons, interventional radiologists, anesthesiologists, physiatrists, palliative care physicians, psychologists, and psychiatrists.

Anyone interested can participate. Just visit the Cancer Pain Research Consortium at centerforthereliefofpain.org or contact me directly.

1987 30th REUNION

Daniel Simon

I was recently appointed president of University Hospitals Case Medical Center in Cleveland. I also received the 2016 American College of Cardiology Distinguished Scientist Award at the recent Scientific Sessions of the ACC in Chicago.

1988

Samuel Wong

After a decade conducting the top orchestras in the world—New York, Japan, and Hong Kong philharmonics; Houston, Seattle, Toronto, Montreal, and Singapore symphonies; and orchestras in Belgium, Italy, and Israel—I have returned to New York City to practice general ophthalmology. In addition to helping the Lighthouse Guild, a leading nonprofit vision and health care organization in New York, to raise money via opera projects, I am also going on surgery missions to Tibet and China and lecturing in music medicine. I am very happy and fulfilled and I am thankful for HMS every day.

2005

David Hwang

Janice Jin Hwang and I are married and having fun with our two kids, Theo, age 5, and Julia, age 3, in Guilford, Connecticut. We're both assistant professors at the Yale School of Medicine, with my appointment in the Division of Neurocritical Care and Emergency Neurology, and Janice's in the Department of Endocrinology. I recently had the pleasure of working with **Michael Hochman '06** to publish a new textbook, *50 Studies Every Neurologist Should Know*, which is part of a series of similarly themed books that Mike is heading up with Oxford University Press. The book contains fifty summaries of landmark clinical trials in neurology and is geared toward medical students and residents who are trying to sort out the language of evidence-based medicine.

Share Your News

If you have updates you'd like to share in Class Notes, you can submit them easily and securely to classnotes@hms.harvard.edu. Be sure to include your full name and class year.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1940s

1942

James T. Blodgett
September 16, 2016

1944

Gaston E. Blom
April 20, 2016

1945

Norman F. Boas
July 19, 2016

Laban W. Leiter
July 1, 2016

1946

Robert V. McCormick
January 25, 2016

1947

Roscoe O. Brady
June 13, 2016

1948

John C. Cobb
June 20, 2016

Richard W. Steenburg
September 19, 2016

1949

James D. Niebel
September 13, 2016

1950s

1950

Rufus K. Broadaway
September 1, 2016

Richard H. Egdahl
April 30, 2016

1952

John D. Constable
June 6, 2016

Chester M. Pierce
September 20, 2016

1953

Charles C. Stamey
September 2, 2016

1954

James E. Boyett
August 2, 2016

Robert B. Pelzel
July 15, 2016

1955

Phillip L. Isenberg
July 20, 2016

1956

Lee G. Miller
April 24, 2016

1957

Gordon F. Lupien
June 7, 2016

1959

John T. Maltsberger, III
October 6, 2016

1960s

1960

Daniel A. Pollen
June 28, 2016

Robert L. Replogle
May 9, 2016

William H. Rickles, Jr.
April 4, 2016

Nicola M. Tauraso
August 7, 2016

1961

Robert Flescher
May 3, 2016

Richard N. Lamb
September 21, 2016

Wilbur J. Springer, Jr.
September 13, 2016

1964

Richard A. Jaqua
July 26, 2016

Bruce L. Miller
June 9, 2016

1965

Mina Farhad
March 16, 2016

Charles B. Smith
August 25, 2016

1966

Alfred D. Steinberg
June 14, 2016

1968

Roland H. Ungerer
March 27, 2016

1970s

1972

Dennis M. McCullough
June 3, 2016

1980s

1983

Kenneth R. First
April 22, 2016

This listing of deceased alumni includes those alumni whose notices of death were received between April 23 and October 10, 2016. Links to full obituaries of these alumni can be found at hms.harvard.edu/memoriam.

If you know of an HMS alumna/us who has died recently, please email the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF YEOU-CHENG MA, CLASS OF 1977

CLAIMS TO FAME

Assistant professor of pediatrics, Children's Hospital at Montefiore at Albert Einstein School of Medicine, Bronx, New York; Executive Director, Children's Orchestra Society, Fresh Meadows, New York

FIRST MOVEMENT

Being a good listener is an asset in music and in medicine, and Yeou-Cheng Ma has applied this skill in both disciplines. Surrounded by music as a child, Ma became a violin prodigy and gave her first recital at age seven. Her interest in medicine developed when she was in college. "I was a chemistry major but felt somewhat unprepared for medical school, partly because I thought of myself as a shy person with limited people skills," Ma says.

DUETS

In medical school, Ma continued her life in music. Mary Howell, the HMS associate dean for student affairs at the time, and the first woman dean at the School, interviewed Ma for admission and later became her advisor. "I learned a lot from her, especially how to mix work with family," Ma says. Howell was herself an accomplished violinist, and Ma invited Howell to play chamber music with her and some medical school friends. Ma says that "in a way, she was my medical mentor, and I was her musical mentor."

In 1994, Ma and Howell played violin together in a group called the Apgar Memorial String Quartet at the annual meeting of the American Academy of Pediatrics. The concert celebrated the issuing of a postage stamp honoring physician Virginia Apgar, who developed the Apgar score, a one-minute test for newborn health. The quartet featured four pediatricians playing string instruments made by Apgar. Ma calls Apgar "one of my medical idols," and says she felt a bond with Apgar through the instrument. "It is great to be connected through either music or medicine." With Howell and Apgar, Ma was able to connect through both.

SMALL CHAIRS

Ma works with children both in her practice as a developmental pediatrician and as executive director of the Children's Orchestra Society.

"In my clinical work, I use music to calm kids down because some of them are quite frightened," says Ma, "especially the little ones. I sing them familiar songs and get them involved in the music, and they soon forget that they're worried."

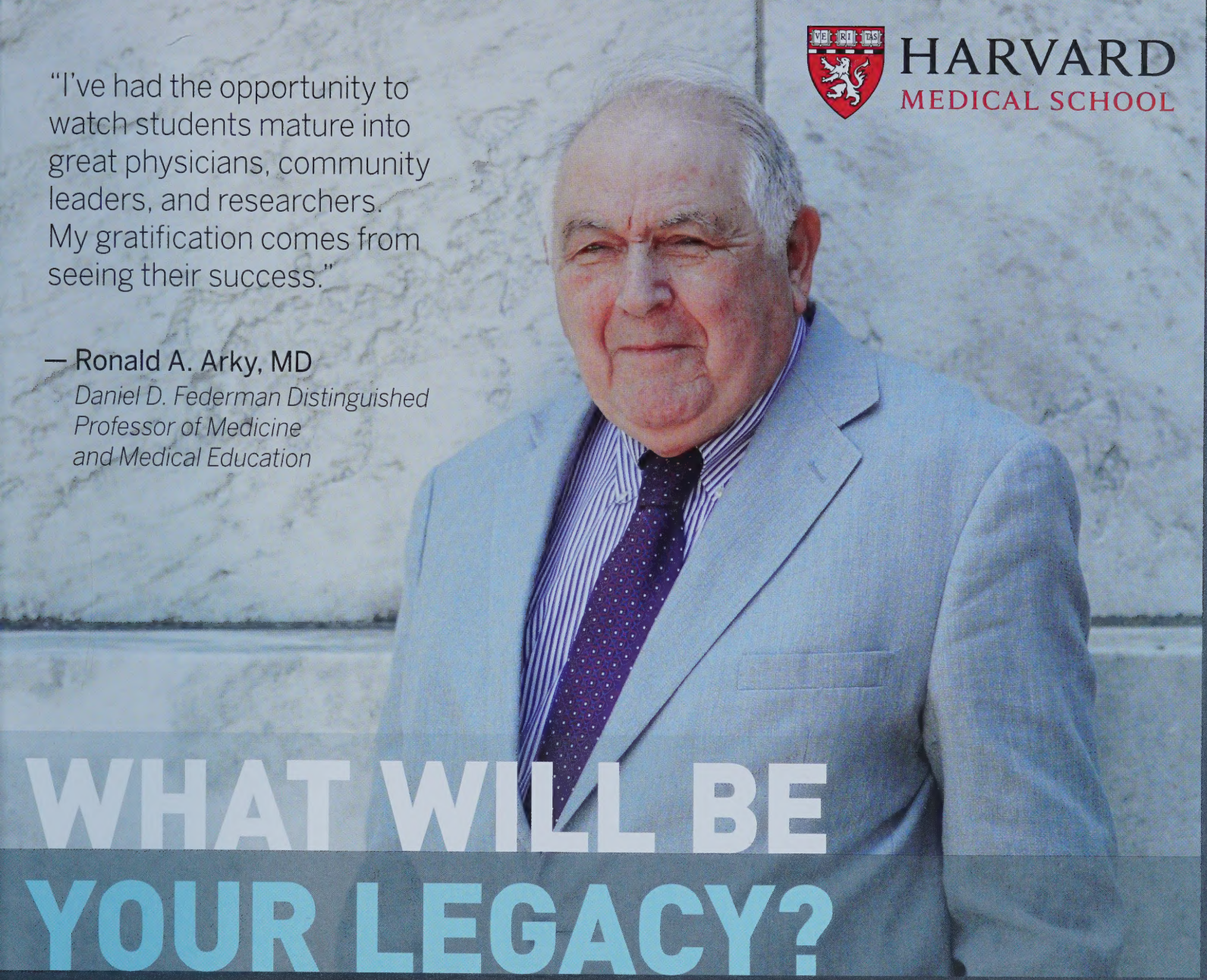
When working with children in the orchestra, Ma teaches them "how to navigate in music so they know how to express themselves through it." Music becomes their outlet for feelings that may be difficult for them to express otherwise.

COUNTERPOINT

When asked whether music or medicine is primary in her life, Ma says, "My husband says that I am a musician who moonlights as a doctor. Music is my first love, and you know how first loves are. They permeate your existence no matter what you do.

"I do love medicine. I love my patients. I love interacting with the patients, their families, and trying to make their life a little better. Compassion, empathy, and the ability to listen make a good doctor and a good teacher."

—Susan Karcz



HARVARD MEDICAL SCHOOL

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— Ronald A. Arky, MD
Daniel D. Federman Distinguished Professor of Medicine and Medical Education

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Ron Arky is an institution at HMS. His most recent gift—a $1 million irrevocable bequest—establishes the Arky Family Associate Director and Advisor of the Francis Weld Peabody Society, which he led for nearly three decades.

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